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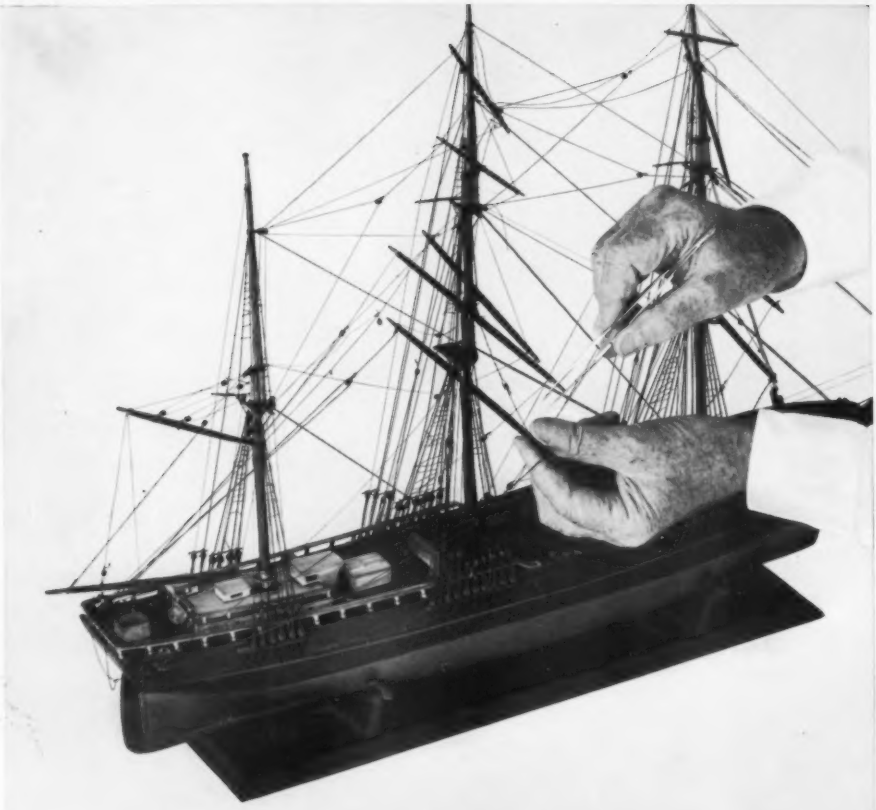

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°Livingston, S., and Petersen, D.: New England J. Med. **254**:327 (Feb. 16) 1956.

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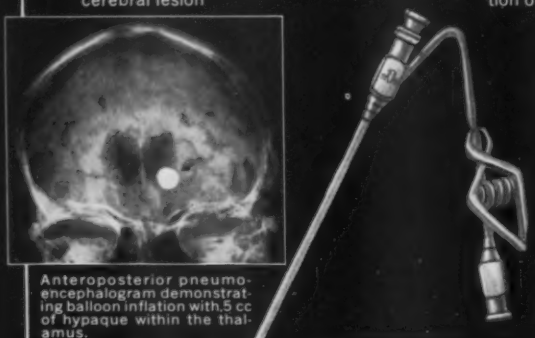

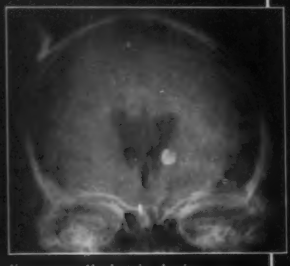

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*Ayd, F. J., Jr.: New England J. Med. *261*:172, 1959.

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*K. R. Magee and M. R. Westerberg, **Neurology, 9**:348, 1959.

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*Khakee, A., and Hess, G. F.: Mellaril in the Treatment of Chronically Disturbed Patients: With Special Reference to Reduced Extrapyramidal Complications, Am. J. Psychiat. 116:1030 (May) 1960.

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Electron microscopic studies of brain tumors

Sarah A. Luse, M.D.

THE APPLICATION of electron microscopy to neoplasms of the nervous system has revealed a number of diagnostic characteristics that are of importance in the identification of tumors. Although a thorough description of the ultrastructural details evident in these tumors is beyond the scope of the current account, it would seem useful to call attention to the diagnostic utility of electron microscopy. This utility stems from the fact that all cellular elements are visible in electron micrographs, whereas, by light microscopy, specialized technics are necessary for the demonstration of separate elements. Moreover, by electron microscopy, cellular organelles can be studied with as much precision as was formerly available for cells and tissues, so that pathologic changes in subcellular elements can now be investigated.

MATERIALS AND METHODS

Biopsies of tumors of the nervous system were obtained at the time of surgery. They were immediately cut into small pieces averaging 1 mm. in diameter and placed in Dalton's osmium tetroxide fixative[1] for one hour at room temperature. The tissues were dehydrated in graded concentrations of ethanol, infiltrated with methacrylate, and embedded in a 7:1 mixture of butyl-methyl methacrylate to which benzoyl peroxide had been added as a catalyst. Polymerization was accomplished at 60° C. overnight. Sections were cut on glass knives in a Porter-Blum microtome. Sections, 1 μ thick, were examined with the phase microscope in order to pick fields for electron microscopic observation. Thin sections were mounted on collodion-covered copper grids and examined in an RCA EMU-2E or 3C electron microscope. Original micrographs were taken on Cramer plates at magnifications of 1,000 to 10,000 diameters and enlarged photographically as desired.

OBSERVATIONS

Glial tumors. *Astrocytomas* were composed of loosely arranged cells, some elongated and others somewhat star-shaped, which were surrounded by an interstitial space apparently

From the Departments of Pathology and Anatomy and the Beaumont-May Institute of Neurology, Washington University School of Medicine, St. Louis.

This work was supported in part by Grants C-2775, B-1539, and B-425 from the National Institutes of Health.

Presented at the American Academy of Neurology, Section of Neuroanatomical Sciences, Symposium on the Pathology of Brain Tumors, April 29, 1960.

filled with fluid. Their margins extended into tenuous processes that often were folded upon themselves and were filled with delicate fibrils. The cytoplasm varied from scant to abundant and contained a variable number of small mitochondria, fibrils, and ergastoplasmic sacs with associated dense granules. Some cells contained cytoplasmic vacuoles which possibly represented early stages of cystic degeneration (Fig. 6). Many of the cell processes were so filled with fibrils that only a narrow rim of peripheral cytoplasm was evident and within them cytoplasmic organelles were scant.

These cells were particularly interesting in their similarity to normal and reactive astrocytes. For the most part, neoplastic processes were more blunt than those of normal protoplasmic astrocytes (Fig. 1) and, in tumors of low malignancy, tended more nearly to resemble the normal fibrous astrocytic cell (Fig. 2). The close resemblance of astrocytic gliosis (Fig. 3) to low grade fibrous astrocytic neoplasia is evident by electron as well as light microscopy.

Tumors which by light microscopy were classified as fibrous astrocytomas had, by electron microscopy, cells with scant cytoplasm and numerous robust processes filled with closely packed fibrils (Fig. 4). In contrast to them were the gemistocytic astrocytic tumors in which the cells had abundant cytoplasm and an eccentric small nucleus (Fig. 5). The cytoplasmic margins of the cells in this latter group extended out into delicate membrane-surrounded processes that were so complexly interdigitated that it was difficult to determine to which cell they belonged. The cytoplasm of these plump cells was filled with small mitochondria, occasional ergastoplasmic sacs, and a multitude of short, haphazardly arranged, fine fibrils which gave to the cytoplasm the homogeneous opaque appearance that corresponds to its almost hyaline eosinophilic character in the light microscope (Fig. 5). Many of the processes isolated from the cell body were even more densely packed with somewhat longer fibrils in orderly array.

Malignant astrocytomas (glioblastoma multiforme). The most common malignant glial tumor may appear in a variety of forms referred to as either glioblastoma multiforme[2,3] or malignant astrocytoma (grade 3 or 4).[4–6] Recently, Russell and Rubinstein[7] discussed the terminology of these tumors and adopted the term malignant astrocytoma but still classified as glioblastoma multiforme that group in which no definite astrocytic forms can be identified. Since the characteristics of the astrocyte family can be delineated by electron microscopy in even this group of neoplasms, it now seems justifiable to consider the 2 terms as synonymous and interchangeable.

The cell population is varied by both light and electron microscopy (Figs. 7, 9, 11, and 12). With the greater magnifications available, there is, however, a similarity of the divergent cellular forms greater than was seen previously because the common characteristics can now be seen. The common findings are those which seem to place a majority of their cells within the astrocytic family. The nuclei of some cells were bizarre in shape and occasionally of giant size (Fig. 9). Mitotic figures, often abnormal, were frequent (Fig. 13). The cytoplasm varied in amount and in some was distinctly fibrous, with numerous robust processes intricately folded upon themselves or interdigitated with those of neighboring cells (Figs. 7 and 8). These processes were usually filled more densely with fibrils than was the cell body proper. Other neoplastic astrocytic cells showed no evidence of fibrous differentiation (Fig. 12). Some cells were identifiable as astrocytes in spite of their bizarre nuclei or abnormal size by virtue of their distinctive cytoplasmic outlines. The outer border of their cytoplasm was formed of redundant folded membranes which at some point were in continuity with the cell membrane (Fig. 12). The cytoplasm of many neoplastic cells was crowded with mitochondria (Fig. 10).

The complexities of vascular proliferation, so noteworthy in these tumors, have yet to be thoroughly studied by electron microscopy. In some, proliferation or thickening of endothelial cells partially occluded the lumen, and, in others, proliferation of adventitia dominated the picture. These alterations will be discussed in greater detail in the description of oligodendrogliomas.

Oligodendroglioma. Normally occurring oligodendroglial cells are satellite to neurons or arranged in rows in the white matter. In electron micrographs, normal oligodendroglia (Fig.

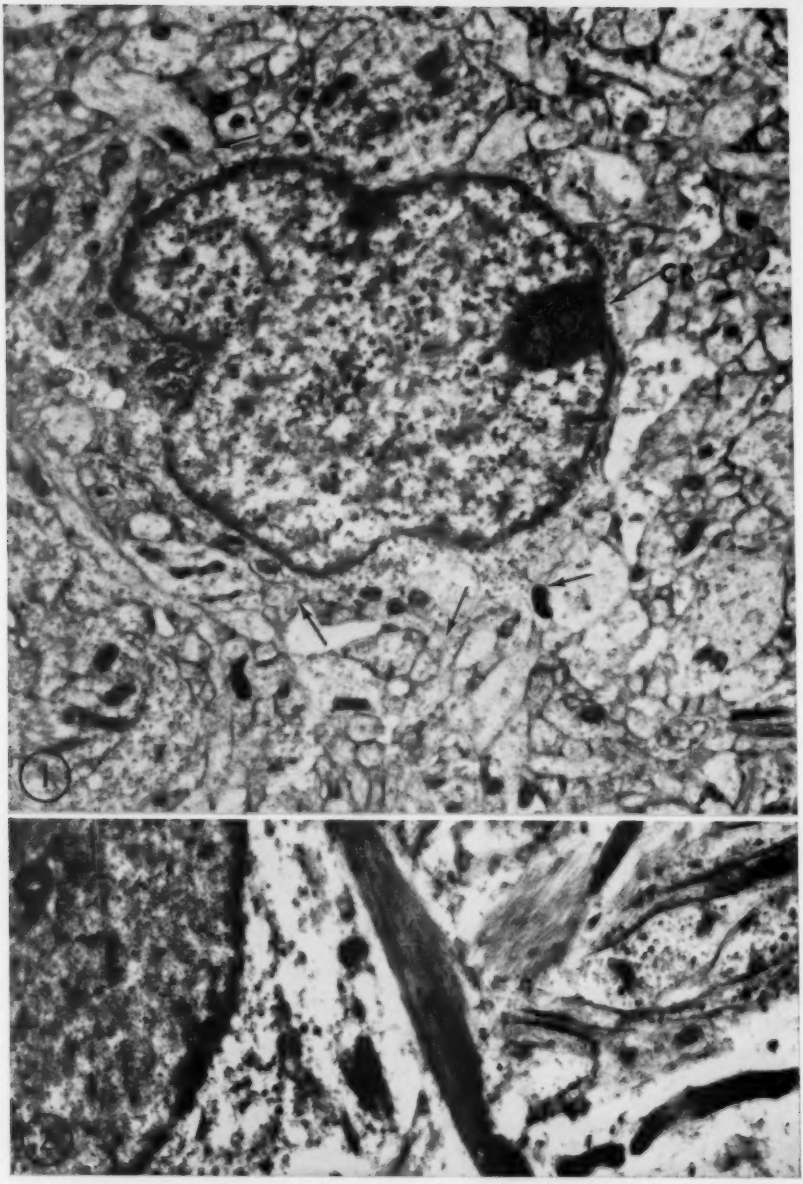

Fig. 1. Electron micrograph of normal protoplasmic astrocyte in cerebral cortex of adult rat. Nucleus is somewhat irregular with a peripheral chromatin mass (CR). Scant perinuclear cytoplasm extends out into numerous plicated, membrane-covered processes (arrows). × 10,000

Fig. 2. Fibrous astrocyte from dorsal columns of adult rabbit. Part of nucleus is evident at right. Dense bundles of intracytoplasmic fibrils course through cytoplasm. Although less prominent than in Figure 1, folded processes outlined by plasma membrane are visible at right. × 15,000

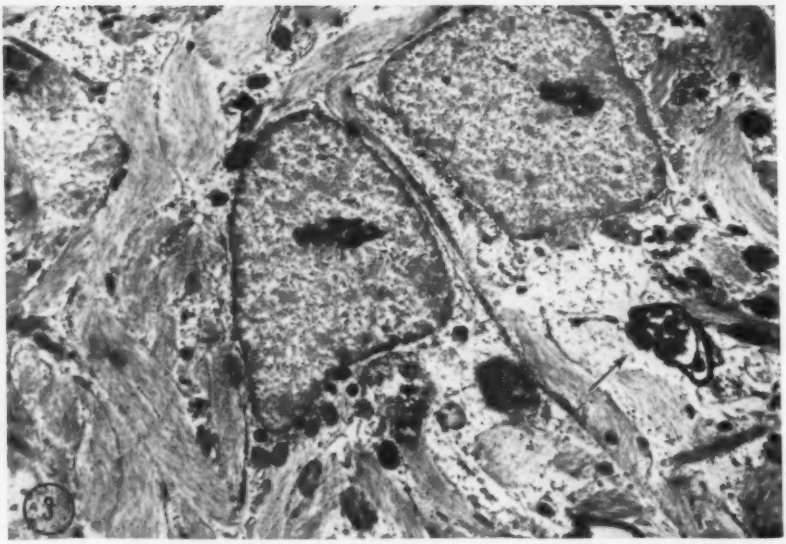

Fig. 3. Electron micrograph from a zone of gliosis produced in cortex of adult cat by injection of alumina gel. Nuclei of 2 hyperplastic fibrous astrocytes are present in field. Both contain nucleoli. At lower right (arrow) is residual myelin debris. Astrocytic processes are broad and almost completely filled with fibrils similar to those seen in normal fibrous astrocytes (Fig. 2). × 6,000

14) possess regular round or ovoid nuclei and abundant pale cytoplasm containing scant ergastoplasm and only a few small mitochondria.[8,9] Oligodendroglial tumors are comprised of similar pale cells, often arranged in nests which resemble a honeycomb by light microscopy because of the sharply outlined cells or cell groups.[10] With the usual aniline stains, their cytoplasm is extremely pale. Electron microscopy of 5 oligodendroglial tumors has revealed a similar picture in all. Their cytoplasm is abundant and pale, with only scant ribonucleoprotein material (Figs. 15, 16, and 20). Both ergastoplasm and Golgi membranes are rare. In some cells, mitochondria are few and small, whereas in others they are so numerous that they are closely packed within the cytoplasm (Fig. 20). Some mitochondria, even in those cells in which they are increased in number, are of usual size. However, often they are enlarged 1 to 2 μ in diameter (Figs. 18 and 19) and sometimes are as large as the nucleoli. Mitotic figures are occasionally present. Foci of electron-opaque, irregularly outlined material are evident within the cytoplasm and have been equated with calcification (Fig. 21). Plasma membranes of neoplastic oligodendroglial cells are sometimes smooth (Fig. 15) and sometimes outline a multitude of short, fine, cytoplasmic processes (Fig. 20) in contrast to the sparse, blunt processes of normal oligodendroglia. Neoplastic oligodendroglial nuclei were small and round to ovoid, with coarsely clumped chromatin. Mitotic figures were not infrequent. Nucleoli of the neoplastic cells often were large and had an unusual pattern (Fig. 17).

The blood vessels of oligodendrogliomas varied from thin-walled capillaries of normal appearance to distinctly hyperplastic vessels similar to those so frequently seen in the glioblastoma multiforme. In oligodendrogliomas, as astrocytomas, there is usually a doubling of the capillary basement membrane, which thus creates a perivascular space in which connective tissue fibers and cells can often be seen.

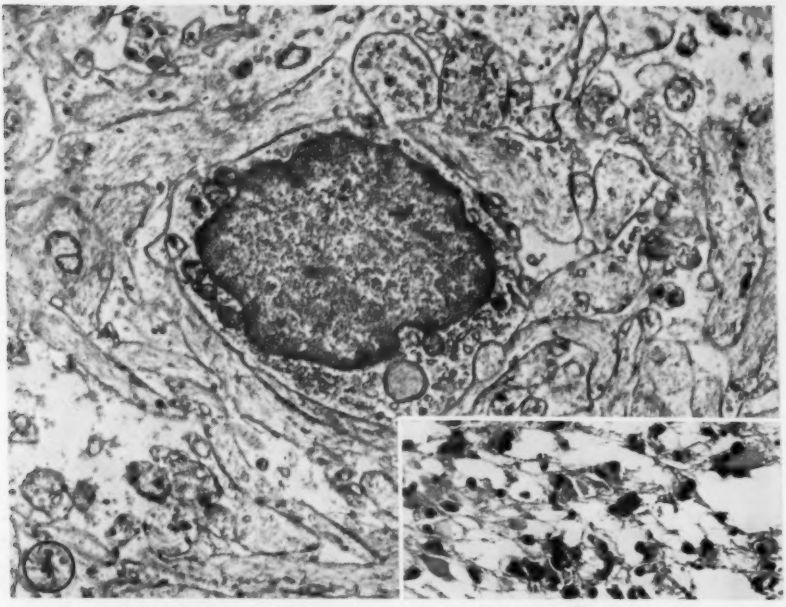

Fig. 4. Electron micrograph of astrocytoma from cerebrum of adult human being. Neoplastic cells were relatively widely separated with uniform small nuclei. Cytoplasm possesses some of the characteristics of fibrous astrocytes because delicate glial fibrils are present and also resembles protoplasmic astrocyte (Fig. 1) in the complexity of its redundant membrane outlined processes. × 7,500. The inset shows the light microscopic appearance. × 250

Such a space does not exist between normal capillaries of the brain or spinal cord and the surrounding neuropil. Although proliferation of endothelium was far less prominent in oligodendrogliomas than in malignant astrocytic neoplasms, adventitial thickening was common. This increase in adventitial cells formed the distinctive vascular anomaly of gliomas (Figs. 22 and 23). Electron microscopy of these abnormal vessels has been particularly revealing. Discontinuities occurred in the external basement membrane that separated the extracellular connective tissue space from the neoplastic cells. Furthermore, at the point of interruption (Fig. 23) of the basement membrane, it extended out along adjacent oligodendroglial cells partially following and outlining their plasma membranes. Thus, basement membrane outlined cells partially within the adventitia of the vessel and partially outside the vessel, so that these cells could be identified as oligodendroglial. Between this outer discontinuous basement membrane and the endothelium of the vessels, multiple basement membranes enclosed the adventitial cells, separating them one from another. The cytoplasm and nuclei of some adventitial cells were distinguishable by their characteristic peculiarities as oligodendroglia. Thus, it would appear that the distinctive hyperplasia of vessels within central nervous system glial tumors is related to a proliferation of basement membrane which encroaches upon and ultimately incorporates the neoplastic glial cells into the vessel wall (Fig. 22).

Ependymoma. In the human being, as in lower forms, the choroid plexus epithelium and ependymal cells (Fig. 24) possess both cilia and microvilli. By electron microscopy, papillomas of the choroid plexus (Figs. 25 and 27)

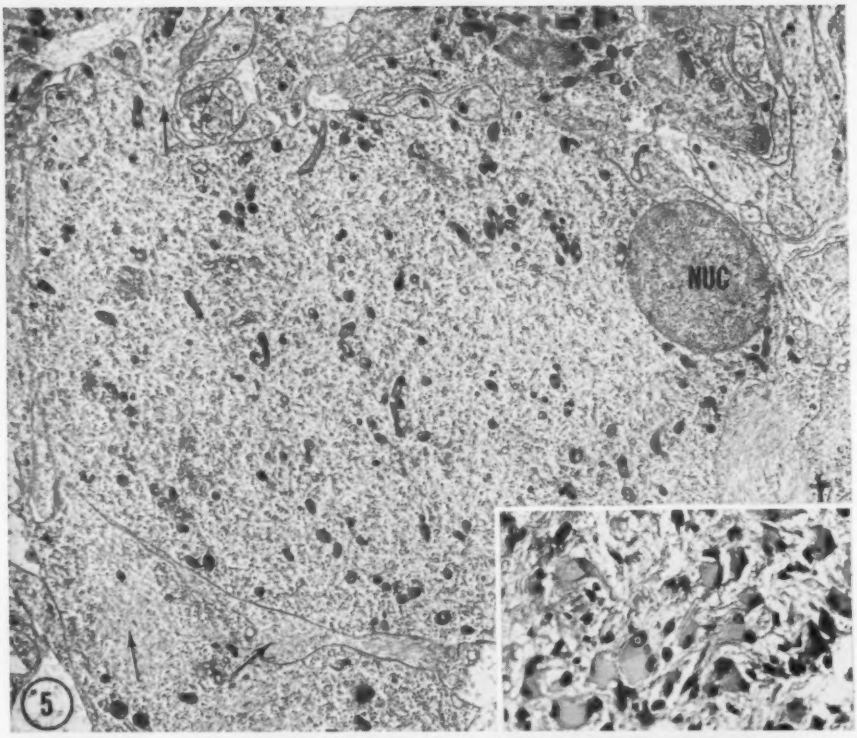

Fig. 5. Neoplastic gemistocytic astrocyte by electron microscopy. Nucleus (NUC) is pushed to one margin of cell. Abundant cytoplasm contains scattered small mitochondria as well as other cytoplasmic organelles. Fine tonofibrils are present in cytoplasm and especially prominent in processes (arrows). × 3,500. Inset shows light microscopic appearance of this tumor. × 250

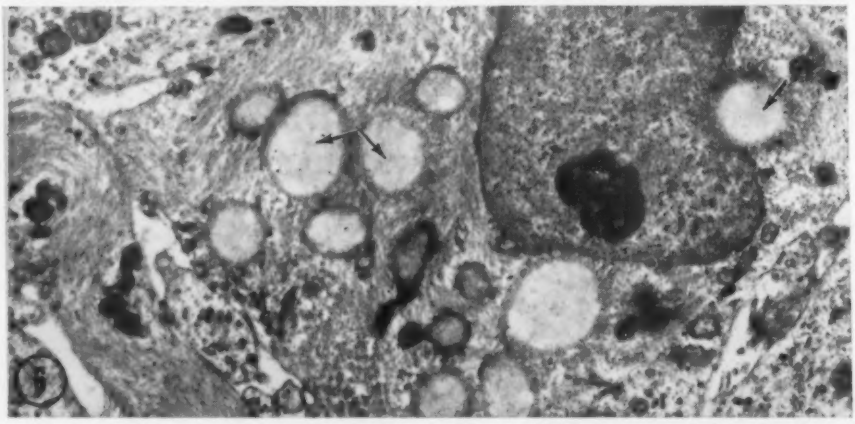

Fig. 6. Within some neoplastic astrocytic cells were microvesicles unrelated to the usual intracytoplasmic organelles. Nucleus of this cell is at right and contains a nucleolus. Origin of vacuoles (arrows) is not known, but they may possibly be the forerunner of cystic degeneration, which is a common occurrence in these neoplasms. × 10,000

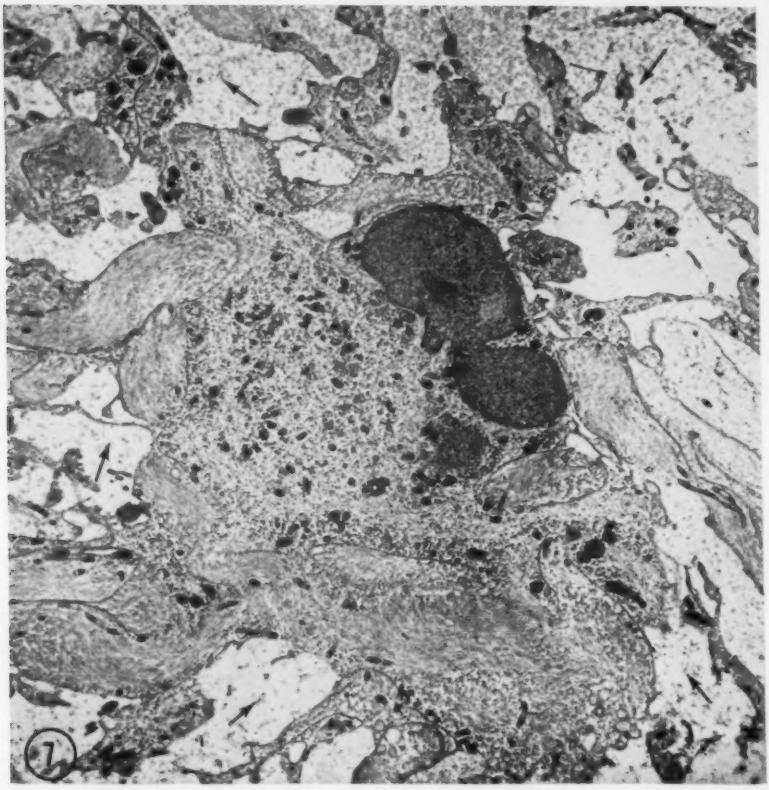

Fig. 7. Electron micrograph from a glioblastoma multiforme (grade 3 astrocytoma) in which nucleus is slightly irregular and eccentrically placed. Abundant cytoplasm to left of nucleus contains small mitochondria. This cell still bears a resemblance to normal astrocytes although processes are more blunt and less folded. Diffuse fibrils are evident in processes. Extracellular space is evident between processes (arrows). × 4,000

also possess definite though scant cilia. Thus, the differential point of absence of cilia or blepharoplasts in papillomas of the choroid plexus is no longer valid.[7,11] In fact, it is entirely possible that, with more experience, the separation of choroid plexus papilloma (Figs. 26 through 28) from papillary ependymoma will depend entirely upon the gross appearance and location, since both are tumors derived from ependymal-type cells.

Well differentiated ependymomas, whether or not of papillary configuration, are readily identified by electron microscopy. They are distinguished by [1] microvilli on the free surfaces of cells, [2] cilia or ciliary rootlets (blepharoplasts), [3] prominent desmosomes (attachment plates or terminal bars), and [4] an abundant cytoplasm with the ribonucleoprotein particles often arranged in a linear pattern. None of these are present in the other glial neoplasms, either benign or malignant.

Those who see histologic sections of brain tumors are aware of the paucity of distinctive criteria for the diagnosis of many malignant or poorly differentiated ependymomas (ependymoblastoma). Some, it is true, are readily

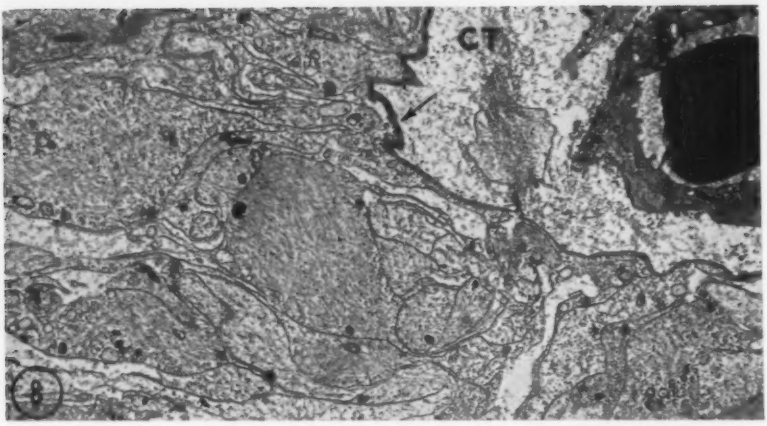

Fig. 8. Electron micrograph of tumor seen in Figure 7. Fibrous character of cytoplasm as it nears a vessel is clearly evident. An erythrocyte almost fills small vessel, which is surrounded by broad connective tissue space (CT). Dense basement membrane (arrow) separates neoplastic glial processes from connective tissue space. × 6,000

recognized, but others are far from distinctive (Fig. 29). It is in this area that the electron microscope and its greater resolution can make a practical contribution to diagnosis of tumors. Cilia, normal or rudimentary, prominent terminal bars, and microvilli have not been seen in any other primary tumors of the central nervous system, and their presence may be used as a diagnostic criteria for the ependymal tumors, however atypical the cells may be in other ways (Figs. 31 and 32). Nucleoli of many neoplastic ependymal cells also were distinctive with a rope-like configuration (Fig. 30).

Nongliomatous tumors. Although it is impossible here to describe all of the nongliomatous tumors of the brain, the main electron microscopic features of 3 groups of these tumors will be presented: [1] meningiomas, [2] neurofibromas, and [3] neurilemmomas.

Meningiomas, as described in detail by Cushing and Eisenhardt,[12] form a family of neoplasms with diffuse histologic attributes. The ones described here fall within the classification of meningotheliomatous or psammomatous meningiomas. The close resemblance of neoplastic meningothelial cells to arachnoidal cells[13] is striking. That these are inherent features of arachnoidal cells is even better demonstrated in the ultrastructure of some of the malignant meningiomas, almost unrecognizable by light microscopy (Fig. 35). The over-all low power picture presented by electron microscopy of meningiomas bears a close resemblance to that of hematoxylin and eosin preparations in which are exhibited whorls as

LEGENDS FOR ILLUSTRATIONS ON OPPOSITE PAGE

Fig. 9. Electron micrograph of a single cell from a glioblastoma multiforme (grade 4 astrocytoma). Most of tumor nuclei were bizarre, as is illustrated in this figure. Some cells and cellular processes showed differentiation toward fibrous astrocytes, as is evident at upper portion of field (arrow). × 8,000. Inset is a light micrograph of this tumor. (× 300)

Fig. 10. Part of another cell from tumor seen in Figure 9. In this cell, cytoplasm is literally packed with mitochondria. Except for increase in number, there is no apparent morphologic abnormality of mitochondria. × 8,000

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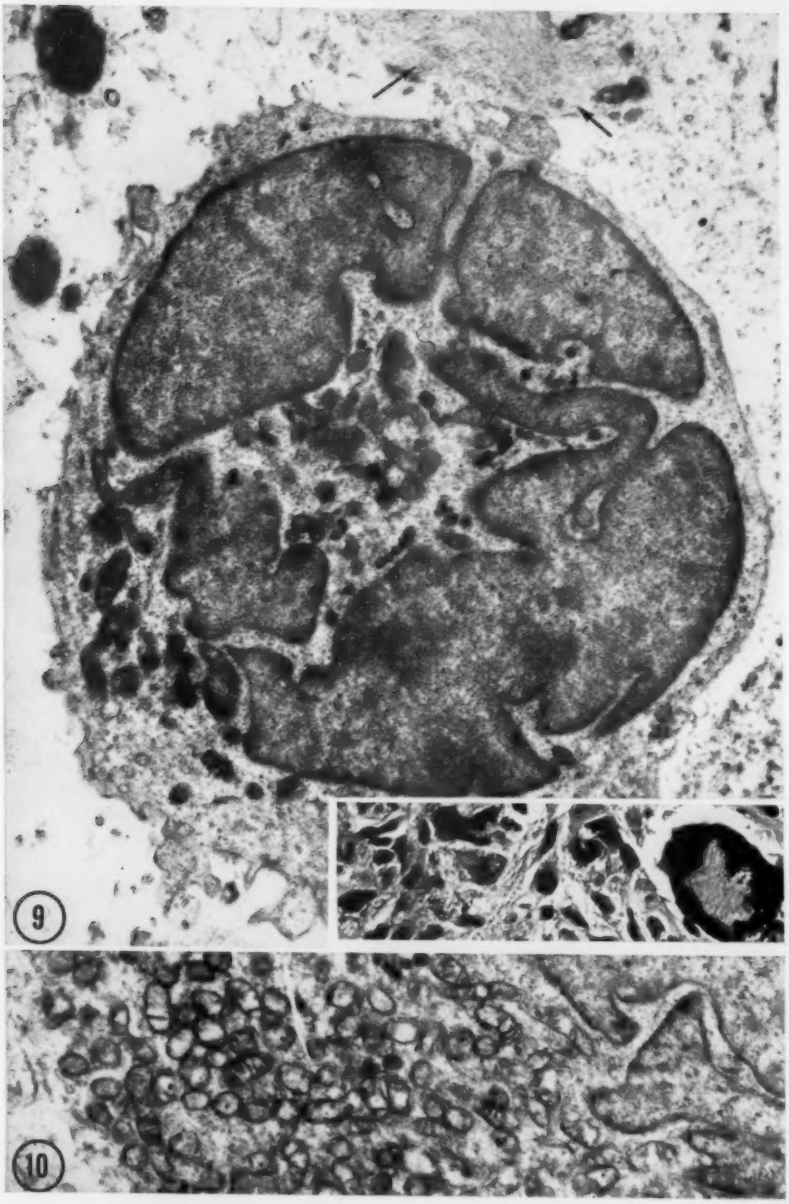

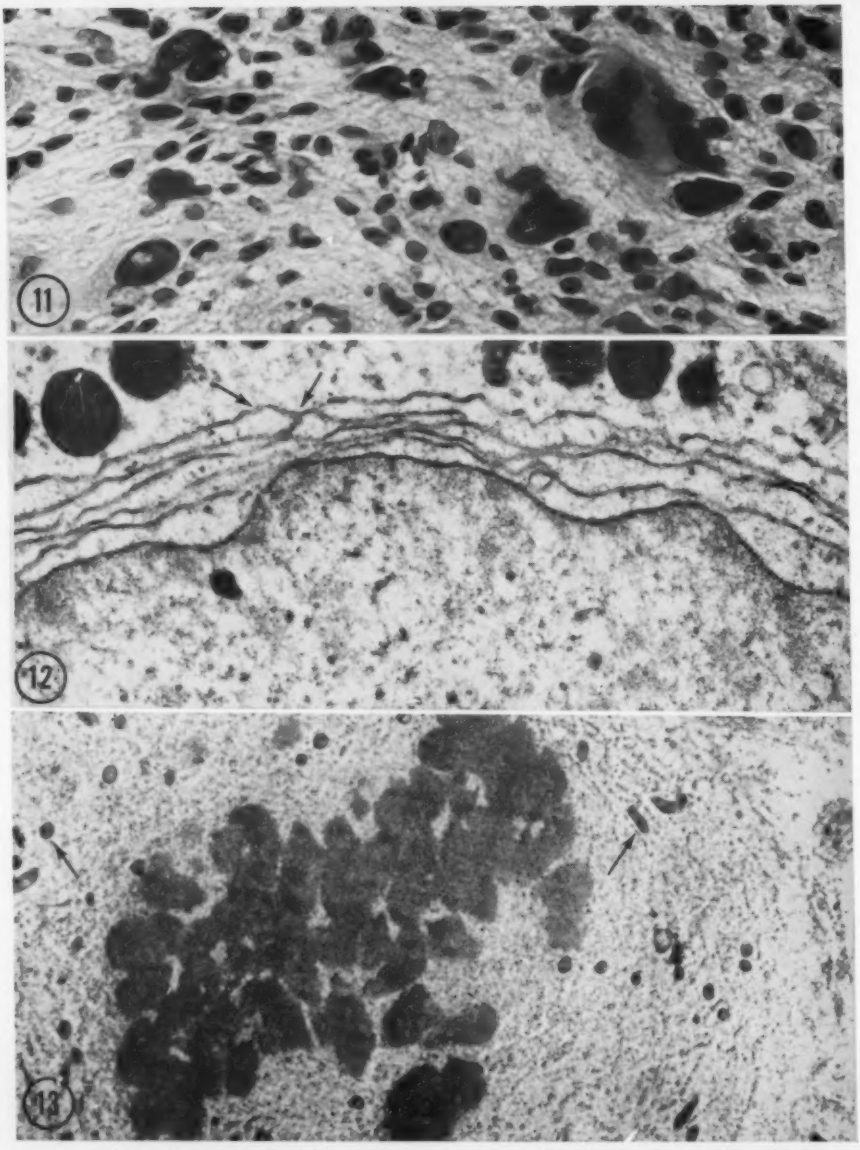

Fig. 11. Light micrograph of glioblastoma multiforme seen in Figure 12. × 350

Fig. 12. Electron micrograph of a grade 3 astrocytoma (glioblastoma multiforme) which differs from those illustrated in Figures 7 through 10 in that there was no evidence of fibril formation. Differentiation was more nearly in direction of a caricature of normal protoplasmic astrocyte with reduplication and folding of plasma membrane (arrows). × 15,000

Fig. 13. Electron micrograph from a malignant astrocytoma illustrates type of mitotic figure frequently seen in these tumors. Note absence of nuclear membrane. Chromosomal material is clumped adjacent to small mitochondria (arrows). × 5,000

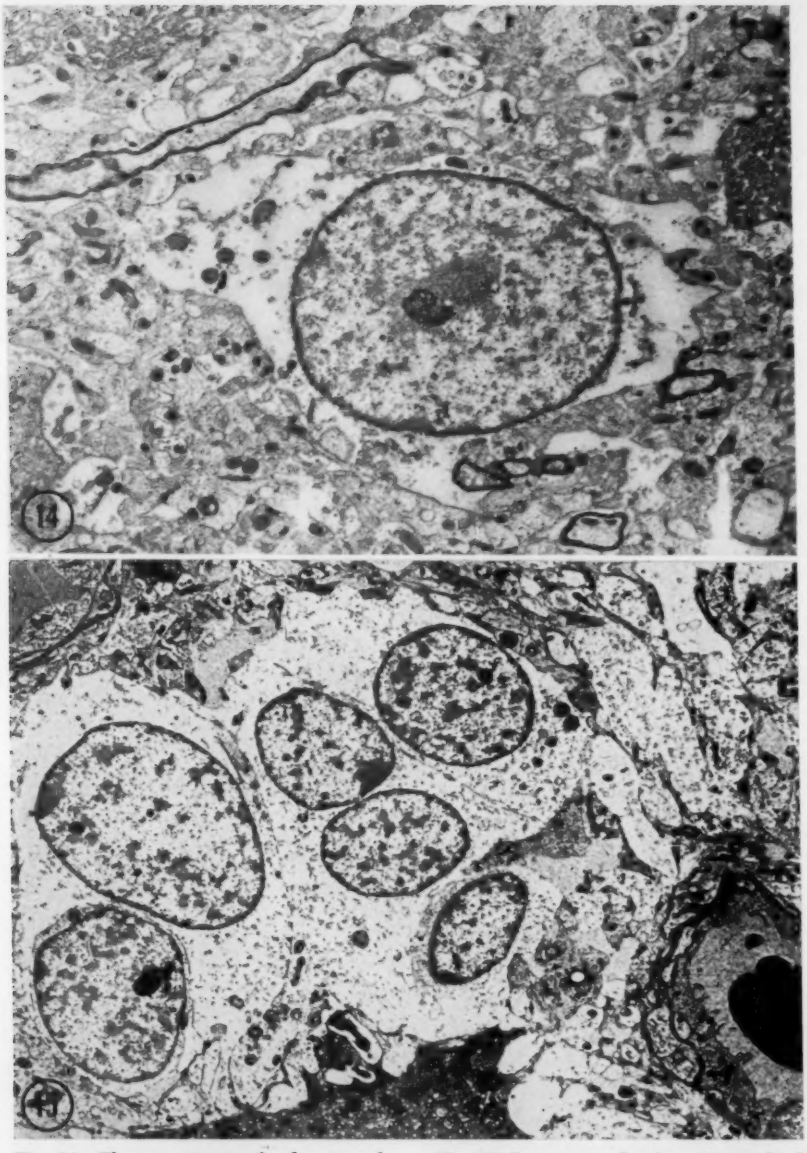

Fig. 14. Electron micrograph of a normal oligodendroglial cell in medulla of adult rat. The central nucleus is uniformly ovoid with a small nucleolus and clump of nucleolar-associated chromatin. The oligodendroglial cytoplasm is pale, with scant ergastoplasm and only a few small mitochondria. × 6,000

Fig. 15. Low-power electron micrograph of group of neoplastic cells in an oligodendroglioma. Nuclei are uniformly ovoid with coarsely clumped chromatin. Pale cytoplasm is poor in organelles and, in particular, ergastoplasm. Portion of small blood vessel containing erythrocytes is present at lower right. × 3,000

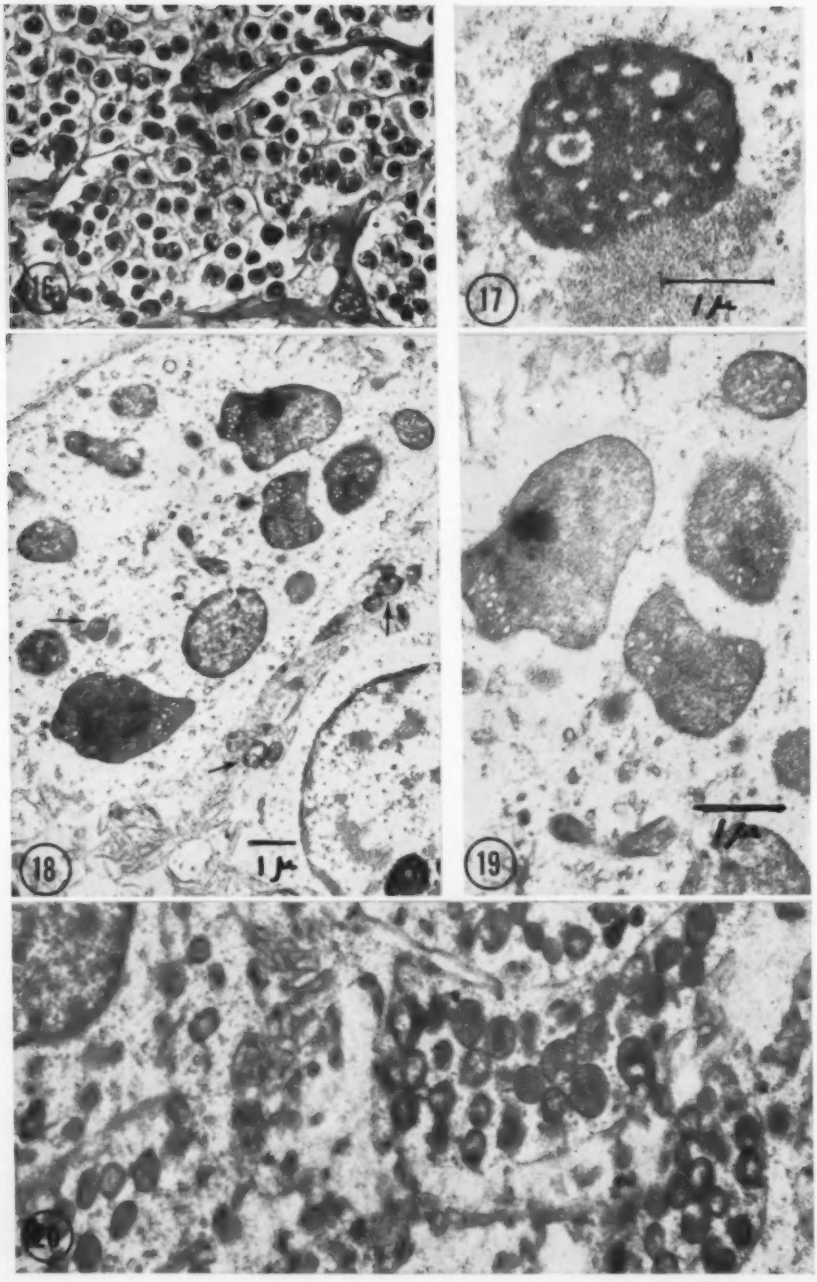
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Fig. 16. Light micrograph of oligodendroglioma illustrated in Figure 15. Classic nests of cells with honeycomb appearance are evident. × 400

Fig. 17. Nucleolus in tumor cell of an oligodendroglioma. This nucleolus is abnormally large (2.3 μ) with multiple, round, pale foci not usually seen in nucleoli of normal oligodendroglial cells. × 17,000

Fig. 18. Low-power micrograph of cell from oligodendroglial tumor seen in Figure 15. A nucleus is present at lower right. Occasional mitochondria of normal size are visible at arrows, whereas multiple, giant, bizarre mitochondria dominate micrograph. × 7,000

Fig. 19. Higher magnification of bizarre mitochondrial forms seen in Figure 18. Cristae are incomplete. Large one at left measures 2.8 × 1.5 μ and contains a dense inclusion. × 14,000

Fig. 20. Slightly higher magnification of another oligodendroglioma. Scattered cells in this tumor, as illustrated here, are densely packed with mitochondria. Mitochondria are of normal size but increased in number. Cytoplasm of cells is pale, with only scant ergastoplasm. × 8,000

well as sheets of cells. The whorls, as is demonstrated in Figure 33, are formed by cytoplasmic extensions of one cell encircling another and two or three cells, in turn, surrounding them. The nuclei and cytoplasm of these cells are in no way unusual, but the cytoplasmic membranes are outstanding. Although the bulk of the cytoplasm does not form processes, the marginal cytoplasm and its covering plasma membrane form short, rounded protrusions that dovetail with those from adjacent cells (Fig. 33). This complicated surface specialization has so far in our experience proved specific for meningiomas. It is even more interesting when one considers that the boundaries of these cells are relatively indistinct by light microscopy. It should be noted that meningotheliomatous cells do not develop a basement membrane, so that the whorls and islands of cells are outlined by plasma membranes alone (Fig. 34).

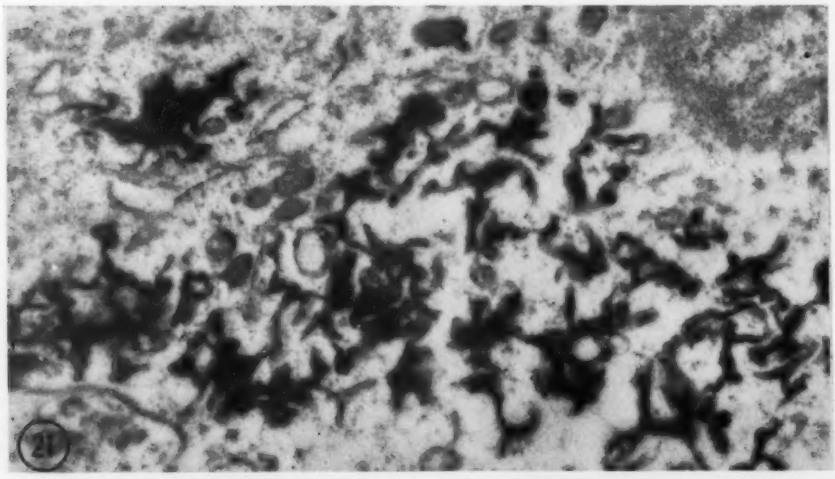

Fig. 21. Electron micrograph of oligodendroglial tumor illustrated in Figures 17 and 20. By light microscopy, calcification was a prominent feature. Cytoplasm of some of the tumor cells contained irregular dense inclusions, such as those seen here, whereas in other cells dense granular material was present. These inclusions are thought to represent precursors of calcium. × 15,000

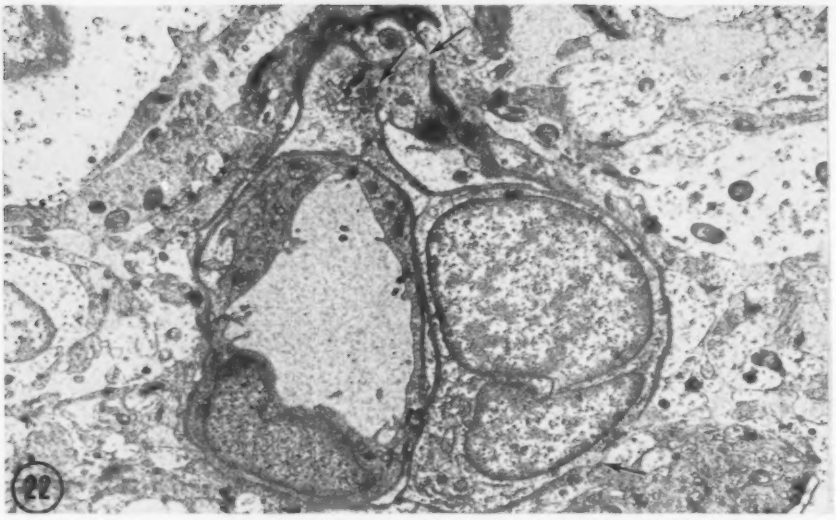

Fig. 22. Electron micrograph of small blood vessel from oligodendroglioma seen in Figures 15, 18, 19, and 23. Large cell with indented nucleus has been surrounded by basement membrane and incorporated into adventitia of vessel. Basement membrane is incomplete at lower right and upper center (arrows). At upper part of figure, basement membrane actually continues out into tumor. × 4,000

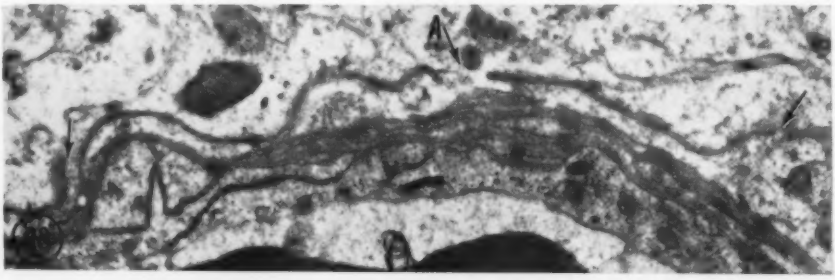

Fig. 23. Higher magnification of another vessel from oligodendroglioma seen in Figure 22. There are 2 red blood cells in lumen. At A, basement membrane is incomplete and neoplastic glial cytoplasm continuous within and outside of incomplete basement membrane. Multiple basement membranes around this vessel suggest that there is an active process of basement membrane formation, the outer one still being incomplete (arrows) and most recently formed. × 12,000

Neurofibroma. The tumors to be described under this heading conform to those designated as neurofibromas by Zimmerman, Netsky, and Davidoff.[14] They occurred on the posterior roots of the spinal cord in patients having other stigmata of von Recklinghausen's disease. By light microscopy, rare axons and posterior root ganglion cells were interspersed within the neoplasms (Fig. 43). The tumors were composed of sparse, irregular, elongated nuclei

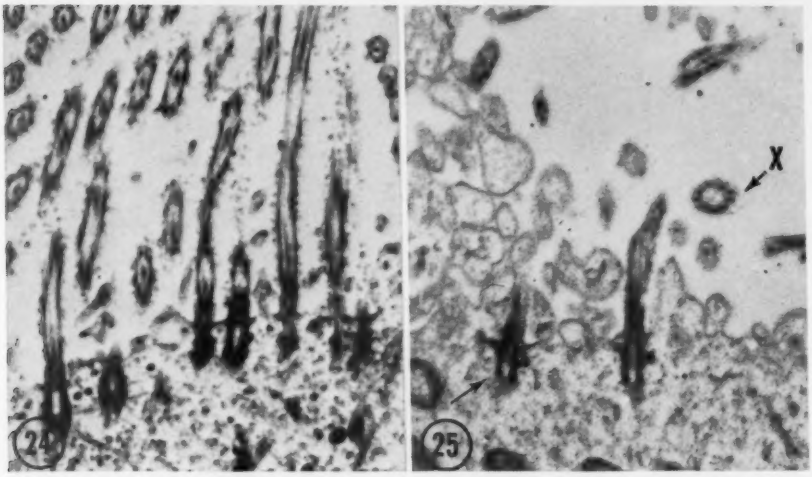

Fig. 24. Electron micrograph of ependymal surface of fourth ventricle of adult cat; 5 cilia with their basal bodies are present. Other cilia are cut tangentially or in cross section. Microvilli are not evident in this particular micrograph. × 17,000

Fig. 25. Electron micrograph of surface of tumor cell (Figs. 27 and 29) in choroid plexus papilloma from lateral ventricle of a child 18 months of age. A rootlet (blepharoplast) of 1 cilium is evident at left (arrow) and another cilium and its root are sectioned longitudinally. Other cilia are seen in cross section (X). Microvilli are numerous. × 17,000

arranged haphazardly in an eosinophilic stroma that stained positively for collagen. By electron microscopy, these tumors were distinctly different from the neurinomas (schwannomas, or neurilemmomas) of the eighth nerve. Neurofibromas were formed by large areas of interlaced collagen fibrils among which were interspersed occasional fibroblasts, Schwann cells, or axons (Fig. 36). The predominant cytologic feature of these tumors was the interlacing collagen fibrils with the usual 640-Å. spacing (Figs. 37 and 38).

Neurilemmomas (schwannomas). The neurilemmal tumors (schwannoma, neurilemmoma, neurinoma, and perineural fibroblastoma) presented a picture entirely different from that of the neurofibromas. The tumors described here arose on either the seventh or eighth cranial nerves or the intercostal nerves. In hematoxylin-eosin–stained sections, these tumors were characterized by [1] interlacing bands of cells with palisading of nuclei, [2] foam cells, [3] hemosiderin-laden phagocytic cells, and [4] foci of degeneration. By electron microscopy, neurilemmomas are composed of cells with abundant cytoplasm that extends into numerous extremely attenuated and complexly interdigitated processes. The surface membrane of the neurilemmal cells differs from that of meningocytes, for even the finest processes of the neurilemmal cells are covered by both a plasma membrane and a basement membrane (Figs. 42 and 45), whereas no basement membrane occurs about meningocytes. In zones where deep clefts occur in the neoplastic Schwann cell cytoplasm, the basement membrane covers the surface of the cell but does not follow the cytoplasmic indentations (Figs. 42 and 45). This appearance is reminiscent of that of hyperplastic Schwann cells forming the tubes of Büngner after section of a peripheral nerve (Fig. 46). The appearance of palisading nuclei (Fig. 41) is no longer prominent at the magnifications employed in electron microscopy. Lipid-laden foam cells are, however, a distinct feature of these tumors. Some fibrils

Fig. 26. Low-power electron micrograph of another choroid plexus papilloma, this one arising in the fourth ventricle. Lumen of blood vessel in core of papilla is present at lower left (BV). Connective tissue space (CT) separates endothelium and ependymal cells. Macrophage cytoplasm and collagen occupy the space. Basement membrane (BM) is present at base of epithelial cells. Their nuclei are almost round. Cytoplasm is abundant with scattered mitochondria and abundant linearly arranged ergastoplasm (ER). Microvilli are prominent on free surface of cells, and terminal bars are evident at margins of cells (TB). × 3,000

of collagen were scattered throughout the tumors and had the usual 640-A. banding. In addition to this, another fibril with a different crossbanding was indentified within the stroma of neurilemmomas and, so far at least, in no other neoplasm or normal tissue. It characteristically was pointed at each end and formed by numerous delicate protofibrils (Figs. 39 and 40). The crossbanding of these fibrils varied between 1,200 and 1,500 A. No definite interpretation can be offered concerning this particular type of fibril except that, so far, it is a characteristic of this tumor alone. The possibility that it may represent an in vivo form of the long-spacing collagen produced at will by Gross, Highberger, and Schmitt[15] in vitro is to be considered.

DISCUSSION AND SUMMARY

In this brief description of the ultrastructural characteristics of some of the more common of the brain tumors, one can only point out distinctive highlights. These distinctions

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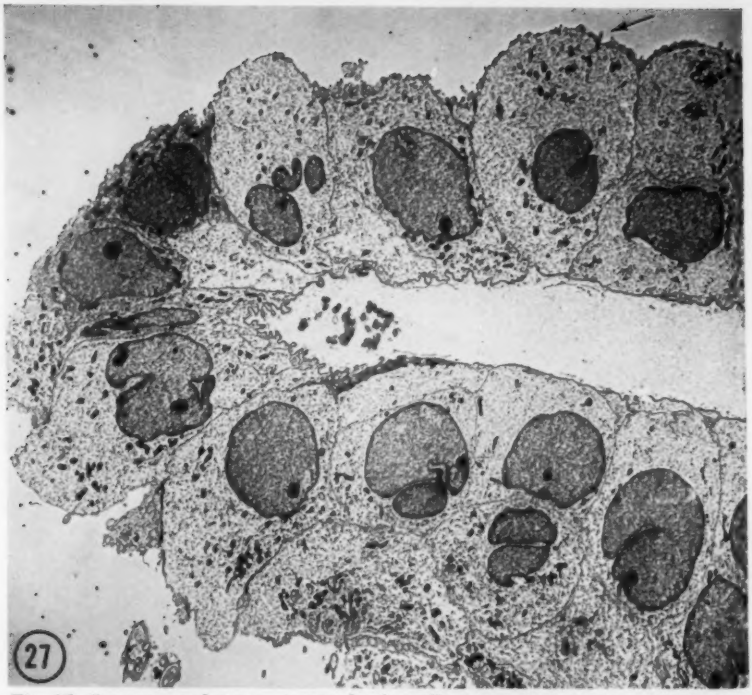

Fig. 27. Low-power electron micrograph of papillary projection in tumor seen in Figure 25. In this section, no vessel is present in central connective tissue core. Plump cuboidal cells have nuclei with an even, finely dispersed chromatin and one or more small, dense nucleoli. Some of the nuclei are irregular with deep clefts. Bases of cells rest on a basement membrane. Free surface of cells is thrown into many delicate microvilli. There is a single cilium (arrow). × 1,500

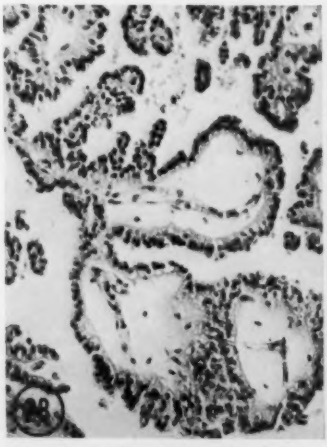

Fig. 28. Light micrograph of choroid plexus papilloma seen in Figures 25 and 27. × 200

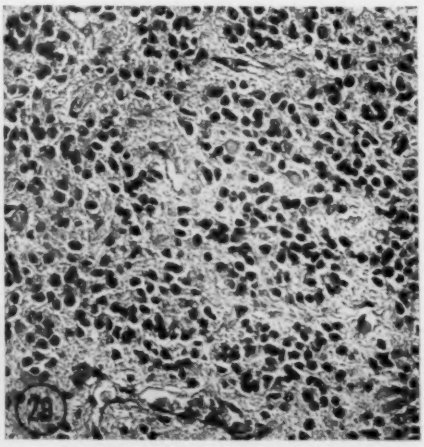

Fig. 29. Light micrograph of ependymoma shown in Figures 31 and 32. × 220

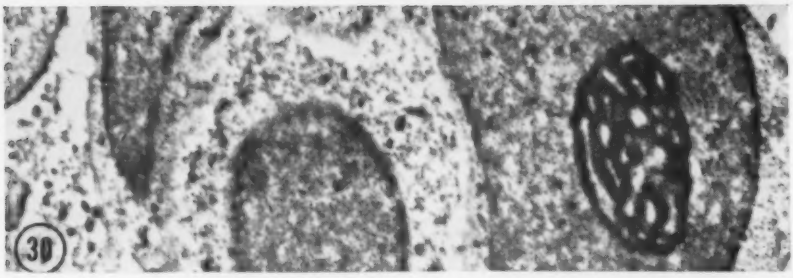

Fig. 30. Electron micrograph demonstrates one of the types of nucleoli in ependymomas. This nucleolus is approximately 2.2 μ in length and has an irregular cord-like appearance. × 15,000

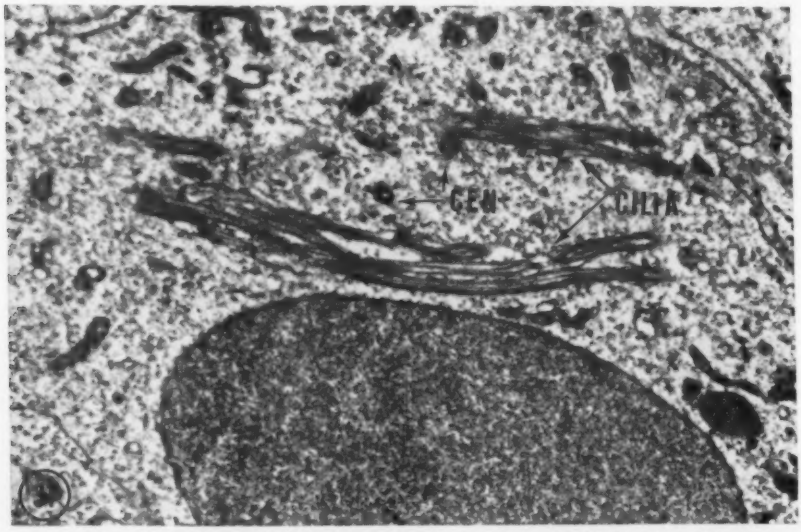

Fig. 31. Electron micrograph of ependymoma shown in Figure 29. Nucleus is ovoid with uniformly distributed chromatin; 2 structures that may represent centrioles are evident at CEN, and 4 abnormal cilia are deeply imbedded within the cytoplasm. × 12,000

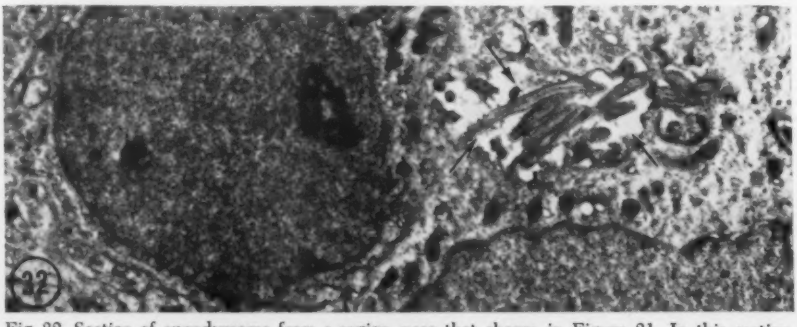

Fig. 32. Section of ependymoma from a region near that shown in Figure 31. In this section, irregular cilia open on a small lumen (arrow). × 10,000

Fig. 33. Electron micrograph of meningotheliomatous meningioma. Parts of 5 cells may be seen. Their nuclei are relatively regular in outline. Characteristic feature in these tumors is complexly plicated interdigitated plasma membranes; 1 cell partially surrounds another, thus forming the whorls. Often, cytoplasm of 1 cell dovetails with that of another. × 8,000. Insert is light micrograph of this tumor (× 300).

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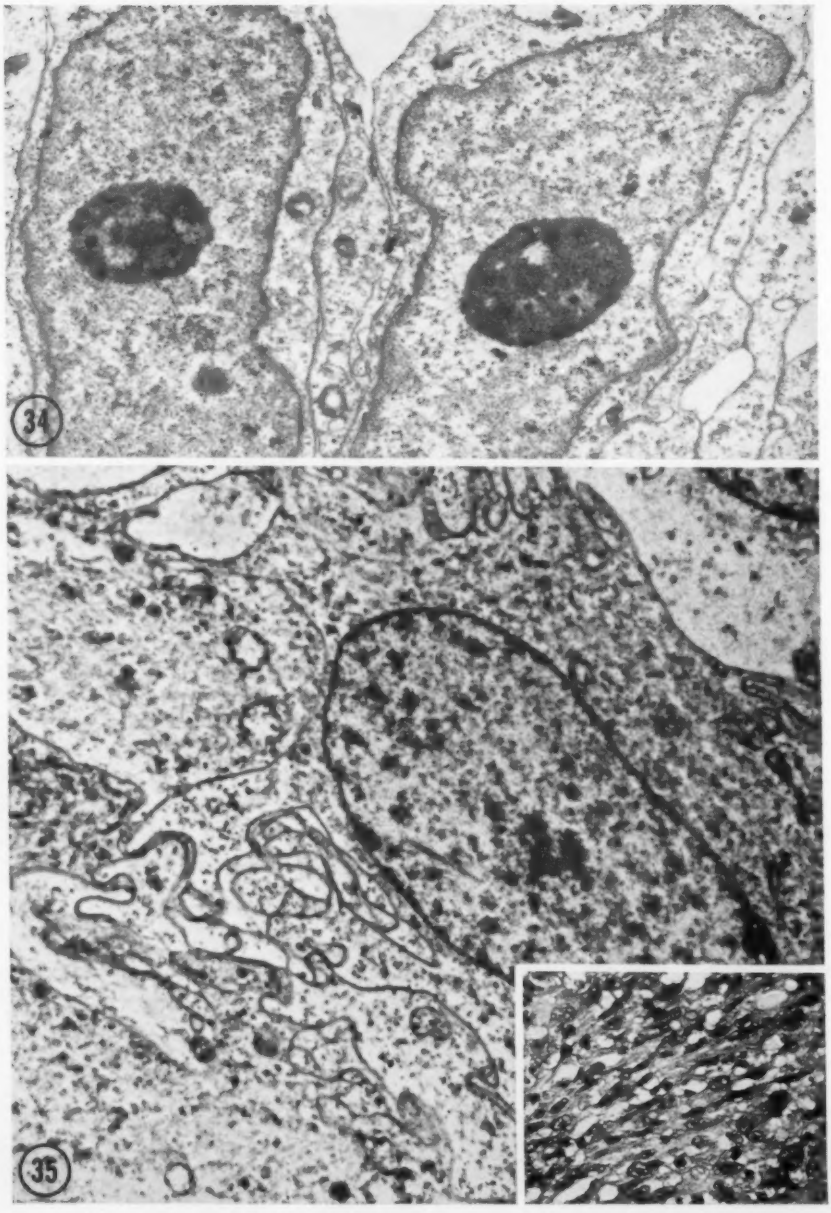

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Fig. 34. Electron micrograph of part of 2 cells from a meningioma. Large, bizarre nucleoli are striking. × 12,000

Fig. 35. Cytoplasmic membrane of cell from malignant meningioma shows interdigitations with its neighbors similar to that seen in Figure 33, which is from a classic meningotheliomatous meningioma. Nuclear chromatin is coarsely clumped. Tonofibrils are present in cytoplasm. Close resemblance of this cell to cells seen in other meningiomas is interesting because, by light microscopy (insert), this tumor was difficult to identify as meningeal. × 8,000

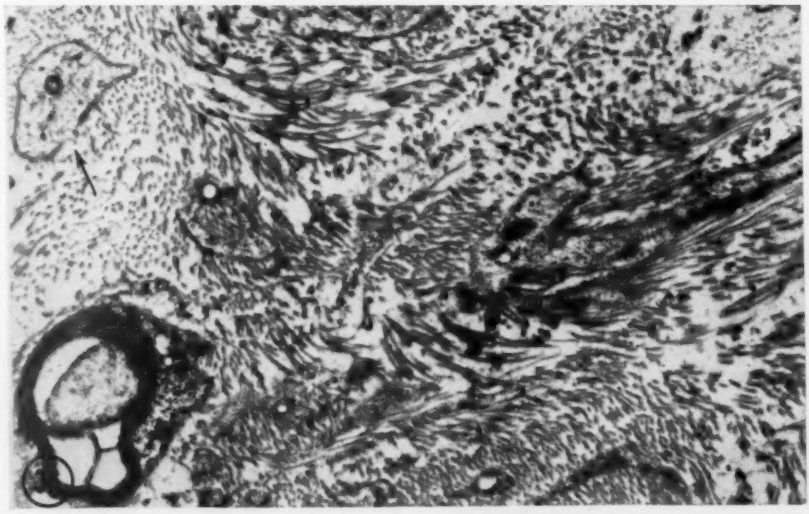


Fig. 36. Electron micrograph of neurofibroma arising in posterior root of cervical spinal cord. Single myelinated axon is present at lower left. Fragment of cytoplasm can be seen at upper left (arrow), and remainder of field is filled with interlacing bands of collagen. × 6,000

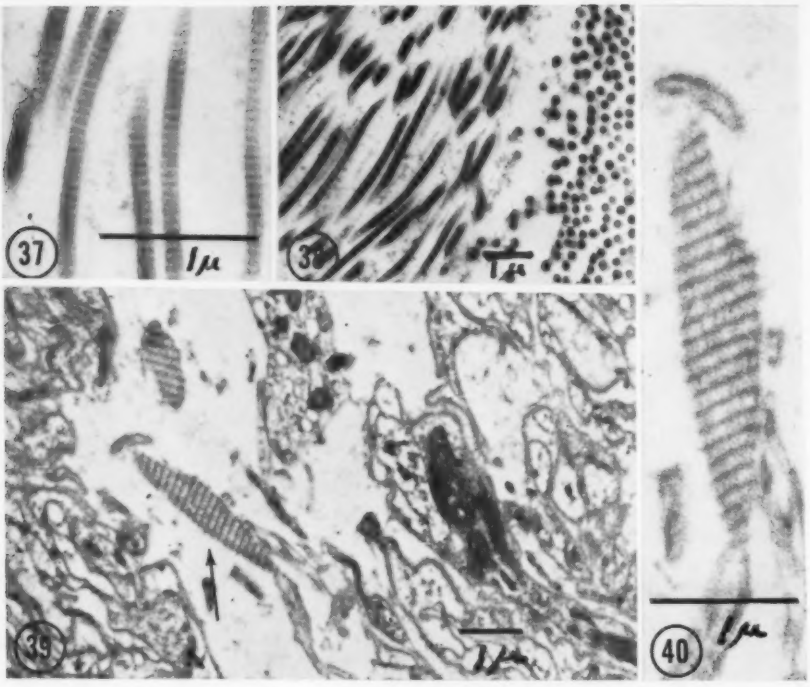


Fig. 37. Higher magnification of collagen in figure 38. This is from neurofibroma seen in Figure 36 and shows usual 640-Å. cross-banding. × 25,000

Fig. 38. Electron micrograph of area from tumor seen in Figures 36 and 37. Much of this neoplasm was composed of sheets of collagen fibrils such as these. × 8,000

Fig. 39. Electron micrograph of neurilemmoma of eighth cranial nerve (see Fig. 43). In many areas, cells were arranged in a palisade. Between cells in some areas were usual 640-Å. collagen fibrils, but, in areas such as this, a peculiar fibril with about a 1,200-Å. periodicity occurred. × 10,000

Fig. 40. Enlargement of fibril in Figure 39. Delicate, longitudinally oriented fibrils have a dense crossbanding of about 1,200 Å. Ends of these fibers were always tapered. Whether they represent an in vivo long-spacing collagen is not known; however, they appear to be peculiar to Schwann cell tumors. × 24,000

LEGENDS FOR ILLUSTRATIONS ON OPPOSITE PAGE

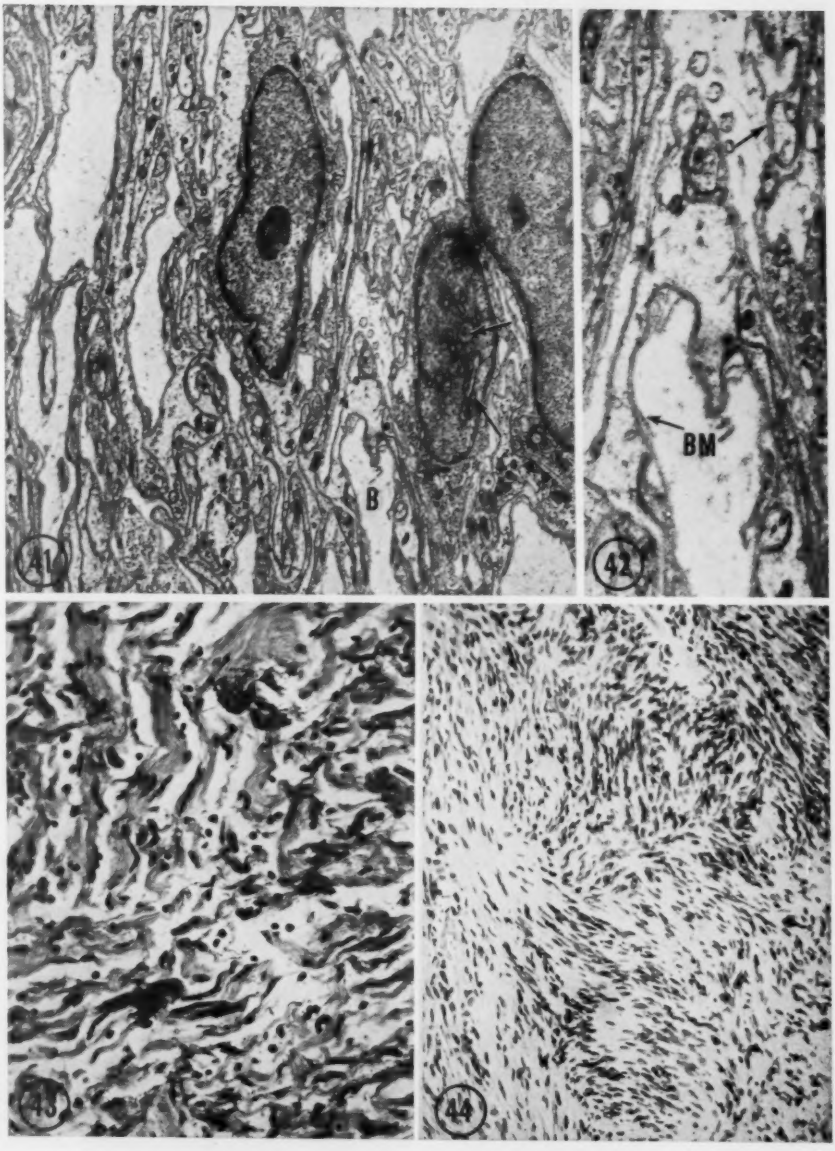
Fig. 41. Electron micrograph from another eighth nerve tumor; 3 nuclei are arranged parallel to each other. Nuclei to left has a large nucleolus. Central nucleus (arrows) has multiple cytoplasmic indentations (or inclusions). Cytoplasm extends out into complexly folded and interdigitated processes. Plasma membranes of these cells are outlined by a distinct basement membrane which is better seen in Figure 42, an enlargement of B. × 5,000

Fig. 42. Enlargement of part of Figure 41 to delineate better basement membranes (BM) which cover cytoplasmic membranes of Schwann cell tumors. × 12,000

Fig. 43. Light micrograph of neurofibroma shown in Figures 36 through 38. × 400

Fig. 44. Light micrograph of eighth nerve tumor illustrated in Figures 39 and 40. × 250

(Legends on page 902)



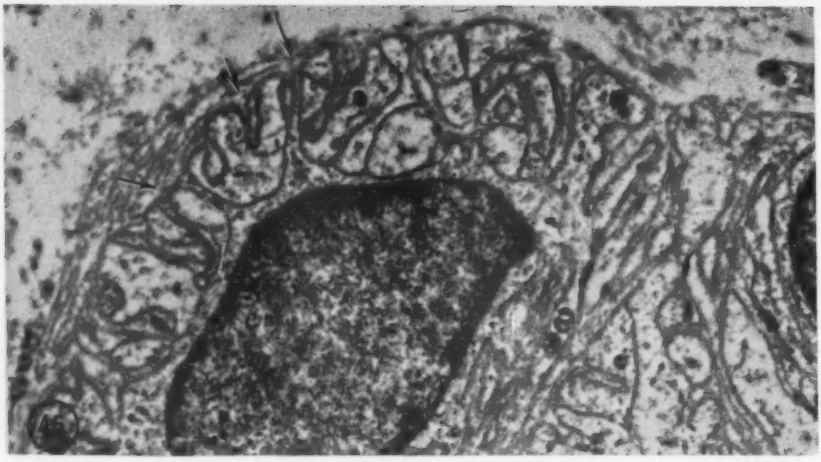


Fig. 45. Photomicrograph of a neurilemmoma of an intercostal nerve from a patient with von Recklinghausen's disease and bilateral eighth nerve tumors. Indentations of cytoplasm (arrows) are outlined by plasma membrane, although sometimes basement membrane also is indented. Similarity of this neoplastic cell to hyperplastic Schwann cell in wallerian degeneration can be seen by comparing Figures 45 and 46. Collagen is present in interstitial space surrounding cell. About × 10,000

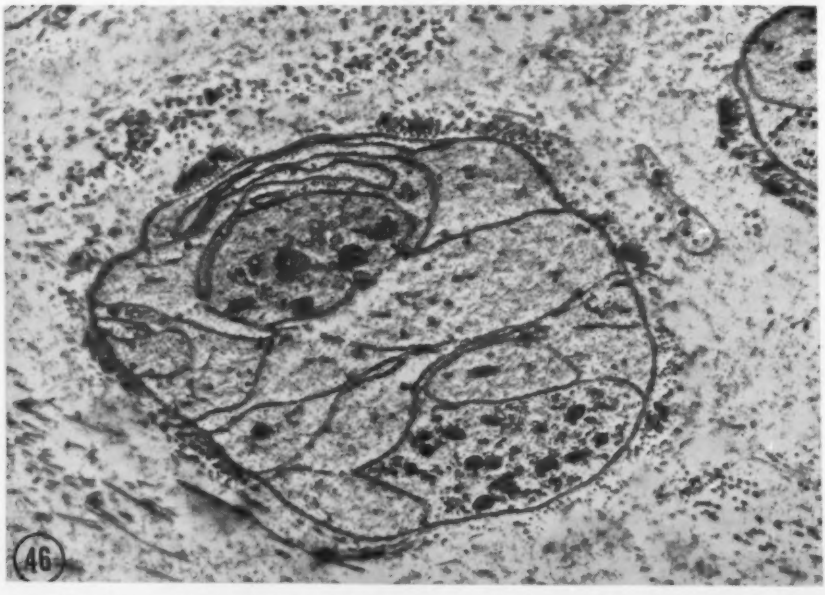


Fig. 46. Electron micrograph from distal segment of a tibial nerve of rabbit forty days after section. Axons and myelin sheath have disappeared, leaving only hypertrophic Schwann cell. Nucleus is not present in this section. Deep indentations of cytoplasm form cytoplasmic compartments. Basement membrane outlines outer parts of plasma membrane. Collagen fibrils are present in interstitial space. × 8,000

are of at least twofold advantage in increasing our knowledge of the nervous system because [1] by studying the neoplastic, the normal cell characteristics are actually seen in caricature, thus helping to substantiate their identification (Figs. 1, 2, 14, and 24), and [2] some sites of submicroscopic abnormality can be identified (Figs. 18 through 20). The latter is of particular importance, for electron microscopy provides a magnification sufficient to identify and study the microorganelles of the cell. An example which may be cited is that of the huge mitochondria of the oligodendroglioma (Figs. 18 and 19). Whether these hypertrophic organelles represent overproduction or an incomplete synthesis of enzymes is not known. Electron microscopy thus can point out a submicroscopic lesion but must, for a definitive answer to this question, be complemented by chemical analysis.

Electron microscopy, tissue culture, and cytochemistry are technics which alone, or correlated, will increase our knowledge of tumors of the nervous system. It cannot be stressed too strongly, however, that none of the information available with these technics should be isolated from the body of knowledge already derived from light microscopy. To do so would ignore the sound correlations between biologic phenomena and clinical observation which have so painstakingly been made by past generations.

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Transient cerebral ischemia in atherosclerosis

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RAPIDLY REGRESSIVE motor or sensory attacks in cerebral atherosclerosis have long been known, but their basis has never been clearly defined. Our current knowledge of cerebral softening[1–4] indicates that some mechanisms underlying these transient episodes have new clinical, pathophysiologic, and therapeutic implications. Their clinical interest lies in their frequency and evidence of some obstructive arterial process. Pathophysiologically, these attacks demonstrate that similar conditions may give rise to episodic ischemia accidents as well as the most severe cerebral softenings. The therapeutic implication is that it might be possible, at the onset of the circulatory insufficiency, to interrupt the progress of the arterial disease or protect the brain from its effects before an ischemic attack has caused irreparable damage.

Our present discussions are limited to these three aspects of the problem: clinical, pathophysiologic, and therapeutic. Also, in this study, we are confining ourselves to cerebral accidents of atherosclerotic origin and shall not discuss other types of vascular accidents such as those resulting from embolism or those associated with carotid sinus, Stokes-Adams syndrome, or migraine.

TABLE 1

NUMBER OF CASES WITH TRANSIENT ATTACKS IN CEREBRAL ACCIDENTS WITH AND WITHOUT ARTERIAL OCCLUSION

	Number of cases	*Number with transient attacks*
Occlusion of the internal carotid	30	16 (53.3%)
Occlusion of middle cerebral artery	31	7 (22.5%)
Without occlusion	44	17 (38.6%)
Total	105	40 (38 %)

MATERIAL AND METHODS

Our series comprises 105 cases of cerebral ischemic accidents studied at the Neurological Department of the Salpêtrière (Table 1). Patient selection is based on three criteria: thorough clinical documentation; study of the cervicocerebral arteries by carotid angiography; and a demonstrable atherosclerotic origin of arterial disease, determined as follows: [1] arterial occlusion shown by arteriography in patients unaffected by embolism of cardiac origin, permanent arterial hypertension, or diseases causing an arteritic process, and [2] cases without visible arterial obstruction (middle-aged or elderly men, elderly women, absence of embolic cardiopathy and arterial hypertension, peripheral arteriosclerosis, and, in some cases, occlusion of the arterial trunks of the lower limbs and coronary insufficiency).

AGE AND SEX

Most of the patients were between 40 and 60 years of age (see figure). The restricted number of patients under 40 is explained in view of the age of onset of atherosclerosis. Patients over 60 are equally few in number because in our selected group are included only those who had an arteriogram performed, so that many of the older persons are thus eliminated.

The age distribution is analogous to that found in patients suffering from cerebral

From the Hôpital de la Salpêtrière, Paris

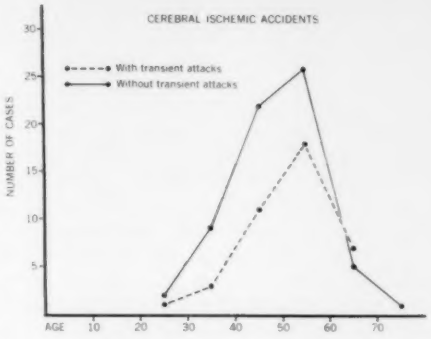
strokes without transitory attacks. It is also strikingly identical in each of the 3 categories based on the presence or absence of arterial obstruction (Table 2). The predominance in men (37 men and 3 women) reflects the greater incidence of atherosclerosis in the male.

SEMIOLOGY OF TRANSIENT ATTACKS

The clinical manifestations of the cerebral attack is obviously linked to the motor, sensory, or psychosensory structures affected by ischemia. They are usually characterized by a partial or complete hemiparesis of central origin, usually recognizable from its topography, a modification of reflexes, and the presence of a Babinski sign. The sensory symptoms that occur include paresthesias and impairments of sensation, especially in the tactile and proprioceptive, localized to half of the body; aphasia may vary from simple suspension to distortions of speech to various forms of the so-called Wernicke's sensory aphasia, depending upon the relative predominance of psychomotor or expressive language disturbances on the one hand or upon receptive and psychosensory disturbances on the other. Hemianopsia may be accompanied by a sensation of mistiness or obscurity of vision.

The symptomatology of these cases needs no further commentary except to mention severity, which varies greatly. Sensory or motor disturbances are sometimes very slight, localized to a lower limb or to the hand and mouth or even limited to the hand alone or to the lips. At other times, there is complete paralysis of half of the body. Between these extremes, there are varying degrees of disability. Similarly, motor or sensory disturbances may be isolated or combined. Such variations depend on the arterial regions of the brain affected. Paralysis of the lower limb appears to relate to the area of the anterior cerebral artery, brachiofacial paralysis with or without Broca's aphasia to the ascending branches of the middle cerebral artery, Wernicke's aphasia to the posterior temporal branches of the same artery, and isolated hemianopsia to the posterior cerebral artery.

The evolution of the ischemic attack deserves attention. The clinical syndrome often appears while during rest, during the night,



on awakening, or in the early part of the day. It may occur also after physical effort or emotional stress. The onset usually is unaccompanied by any particular circumstances. paralysis and paresthesias may begin in a limb and, if the process extends, may progress rapidly.

Complete preservation of consciousness is one of the striking clinical features (34 cases, 85%). Occasionally, the patient experiences slight discomfort. The duration of these episodes vary considerably from patient to patient and in the same patient. In most cases, there is rapid improvement from the attack followed by complete recovery from one-half to a few hours after the onset. In other cases, the duration of the episode is even shorter, lasting from a fraction to a few minutes. In a few cases, however, the attack may be more prolonged, persisting for several days.

In a short attack, the disturbance has the characteristic of a paroxysmal phenomenon and may be diagnosed as a focal epileptic seizure. This occurs only when the ischemic attack is manifested by ascending paresthesias or aphasia and lasts only a few minutes. Ob-

TABLE 2

AVERAGE AGE OF PATIENTS

	With transient attacks	*Without transient attacks*
Occlusion of the Internal carotid	52	52
Occlusion of middle cerebral artery	50	48
Without occlusion	50	49

viously, paralysis cannot be regarded as an epileptic process in the absence of tonic and clonic phenomena. It should be borne in mind, however, that certain transitory ischemic attacks may manifest themselves in epileptic seizures. These are not frequent. We have observed them in 7 cases (4 internal carotid obstructions, 1 middle cerebral obstruction, and 2 cases without obstruction). The seizures were focal, generally motor and sensory (6 cases). In 5 of the cases, they preceded major cerebral strokes, and, in 4 cases, they were the only clinical expression of a circulatory disturbance before the major attack.

These observations briefly summarize the semiology of these transitory disturbances of the brain. We cannot fail to recall, however, that similar phenomena have been observed in the course of atherosclerosis of the vertebrobasilar system. In the latter instance, however, they are more frequent[5] and are marked by a greater variety of clinical disturbances: paralysis, paresthesias, vertigo, diplopia, ptosis, dysarthria, dysphagia, auditory disturbances, motor or sensory impairment of half the face, and, also, impairments of vision, the last being associated with circulatory disturbances in the region of the posterior cerebral artery.

It is not always easy to differentiate cases in which the vertebrobasilar system is affected from those affecting the carotid circulation. Bilateral involvement of the body, disturbance of functions peculiar to the brain stem, and deterioration of consciousness constitute the most valid signs for localizing brain stem ischemia. The nature of these episodes is quite similar to cerebral attacks, and they give rise to the same etiologic and pathophysiologic problems. They differ only in the location of the arterial process.

RELATION TO ATHEROSCLEROSIS

How are these transitory ischemic attacks related to the evolution of atherosclerosis? To this question, an answer cannot be depicted schematically because of the great variation in the number of attacks, the mode of their evolution, and the rate of recurrence.

Nevertheless, in our series, the frequency with which these episodes occur in association with atherosclerosis are indisputable. Among 105 patients we observed, these episodes appeared in 40 (38%). The distribution of these patients in relation to the presence of atherosclerotic occlusions is as follows: 16 of 30 with transient attacks (53.3%) demonstrated an occlusion of the internal carotid artery, and 7 of 31 (22.5%) with transient episodes demonstrated an occlusion of the middle cerebral artery. Of 44 patients, 17 with transient attacks (38.6%) did not demonstrate in arteriographic studies conclusive evidence of occlusion of a principal arterial trunk (Table 1). That is to say, 23 (57.5%) of 40 patients who had one or several transitory attacks demonstrated an occlusion of either the internal or middle cerebral artery.

In the series, 98 patients showed signs of brain softening with more or less severe after effects. Of these, 33 (33.6%) previously had one or several transitory attacks. In 7 of the 98 patients, these attacks completely subsided. In this general picture, the frequency of transient attacks in the evolution of arterial occlusion and in the history of cerebral softening is obvious. Some details should be emphasized concerning their interrelations.

In the great majority of cases, the transitory ischemic attacks arise in arterial regions that later become the site of infarctions. However, recurring transient episodes do not always follow the same clinical pattern in a given patient. Commonly, for instance, the transient premonitory signs of left middle cerebral softening are aphasia or paresthesias alternating with transitory hemiparesis. Recurrent attacks may affect first an upper limb and then the lower limb before a major stroke appears involving the entire half of the body. Some patients with recurrent episodes experience paresthesias confined sometimes to the angle of the mouth but at other times extending over a much larger area of the body. The ensuing cerebral softening affects the entire arterial area from which the various transitory ischemic episodes arise. Exceptionally, transient attacks arise from cerebral areas outside the area of softening. One of our patients had an anterior cerebral artery syndrome in association with an obstruction of the internal carotid artery. Three months previously, he had a major attack of focal motor seizures limited to the face and upper limb.[6] Both injured areas were dependent for their blood supply on the internal

carotid, but the evolution of the ischemia followed this usual pattern.

The number of transient attacks and the intervals between them and between major ischemic strokes vary widely. Rarely, numerous (several dozen) transient attacks may occur for days or weeks, months or years preceding an infarction. There are, of course, many variations of the time intervals between the transient attacks and of the time intervals between the transient and the major attacks. In 22 cases of carotid or middle cerebral artery obstruction, the transient symptomatology preceding the major attacks was a matter of days or weeks in 7 patients, of months in 8, and of years in 7.

The ischemic attacks occurring shortly before evidence of softening often present a unique pattern of sensory or motor symptoms that last a few minutes but recur frequently. When ischemic attacks cover a period of several years, they may occur less frequently but are more severe. An example of each of these syndromes is illustrated in these two case histories:

Over a period of three months, a man of 36 (Schv.) had complained of numerous attacks of tingling sensations in the right hand that lasted for a few seconds. Then, one day, he experienced a violent headache and generalized discomfort of short duration. Next day, while driving his car, he felt tingling in the right hand for a few seconds and then right hemiplegia with aphasia developed. Seven hours later, he had improved so much that he had only moderate difficulty in pronouncing certain words. However several hours later, while getting up, the patient again had hemiplegia and aphasia that persisted. Arteriography demonstrated an obstruction of the left internal carotid artery at its origin.

A man of 37 (Wip.) had abrupt onset of aphasia that completely disappeared in two days. Ten years later, he had sudden loss of speech which cleared entirely in six days. A year later, the same disturbance of equal duration reappeared. Fourteen years after his first attack of aphasia, he again suddenly experienced aphasia and apraxia that lasted two weeks. He had two relapses in the following month which left only aphasic sequelae. Arteriography revealed obstruction of the left internal carotid artery at its origin.

These two cases are cited to demonstrate the evolution of these transient attacks, but it must be borne in mind that the syndrome may appear in a variety of forms. The next rare type of case illustrates the extent of this diversity.

A man of 40 (Ha.) noticed from time to time the sudden appearance of paresthesias that began in the left hand and extended to the upper limb; these attacks lasted less than a minute and, in the course of time, became less frequent. They recurred about 10 times at varying intervals for five years, when the paresthesias migrated to the lower limb from the thigh to the foot. They also became more frequent, recurring weekly at first, then daily, and, finally, several times a day. When examined, the patient had experienced several hundred of these attacks. The clinical examination and electroencephalogram were normal. Right carotid arteriography showed no obstruction. Two months later, the patient experienced a mild left pyramidal syndrome lasting a few days. Some days later, severe hemiplegia suddenly developed. Arteriography performed on the same day showed complete obstruction of the middle cerebral artery at its origin. Two days later, the patient became comatose and died. Postmortem examination revealed an extensive thrombosis of the right middle cerebral artery with massive infarction in the region of its blood supply. The severe hemiplegia probably dated from the time of the arterial occlusion, and it is certain that the fleeting attacks of ischemia recurring over five years were in some way related to the evolution of the arteriosclerotic process.

Almost half of our patients who were afflicted with arterial occlusion had one or more of these transient attacks, but they occurred more frequently in those showing obstruction of the internal carotid artery (16 of 30, 53.3%) than of the middle cerebral artery (7 of 31, 22.5%). This is due to establishment of a more efficient collateral circulation in patients with carotid artery obstruction than in those with obstruction of the midle cerebral artery.

So far, we have considered only cases in which transient attacks have appeared as the first sign of an obstructive arterial process which, after a varying duration, ends in a major stroke. However, in other cases, these transient ischemic episodes seem to be the only cerebral manifestations and, in spite of occasional recurrences, do not terminate in a permanent disability. The following case is illusrative.

During the night of July 21-22, 1958, a man of 55 (Ar.), when endeavoring to get up, fell because of weakness of the left lower limb. He recovered from this condition in a few minutes. The next day, after lunch, he suddenly felt a sense of discomfort with weakness of the left half of the

body but no subsequent loss of consciousness. This episode lasted three minutes. On the morning of July 23 and again that evening, the same type of attack recurred. The next day similar paralytic paroxysms of the left half of the body were present at 8:00, 9:00, 9:10, and 10:00 P.M. He was admitted to our Neurological Department on July 26, after one of these episodes. Clinical examination was normal, and no focal electroencephalographic disturbance was observed. Right carotid arteriography did not show any obstruction.

It might be supposed that, in a case of this kind, a major stroke could be anticipated in the future after the arterial obstruction had become complete. This, however, is not always true because the symptoms of occlusion of the internal carotid artery usually consist of only one or a few ischemic attacks followed by recovery. This indicates that, under certain circumstances, an arterial occlusion may occur without any circulatory derangement other than slight and intermittent ischemia. We have recorded elsewhere[7] a case of bilateral internal carotid artery obstruction (Ste.) illustrating the extent of the adaptation of the cerebral circulation to these conditions. Although less frequently observed, this kind of circulatory compensation is occasionally found after occlusion of the middle cerebral artery. Here is an example.

A man of 38 (Stu.) had right hemiparesis with aphasia. Carotid arteriography demonstrated obliteration of the middle cerebral artery at its origin. Recovery from his condition was rapid and almost complete. A year later, the right hemiplegia suddenly recurred but subsided in three days.

However, there are numerous cases in which periods of transitory attacks are followed by cerebral softening without evidence of any arterial obstruction as revealed by arteriography. This was noted in 11 of our 44 patients.

Subsequently, it appears that the transient disturbances or even the cerebral lesions cannot be explained merely as due to organic alterations of the arteries.

To summarize, transient cerebral ischemic attacks precede, accompany, or follow the obstruction of a large arterial trunk. This train of events is best illustrated in occlusion of the internal carotid artery but may also happen in obstruction of the cerebral arteries proper. These attacks demonstrate the progressive evolution of the atherosclerotic process before the vessel is completely occluded, which is most frequently the case. They may also indicate intermittent insufficiency of a compensatory circulatory system, usually adequate though frail, which has developed as the result of the arterial occlusion. In the evolution of atherosclerotic disease, the transient attacks most frequently precede any cerebral softening but do not necessarily point to its imminence because, in some cases, they constitute the sole cerebral manifestations of arterial disease.

PATHOPHYSIOLOGY

Traditionally, cerebral vasospasm was held responsible for these attacks. This may seem adequate to account for the appearance and sudden disappearance of signs which are undoubtedly the result of ischemia but which are so fleeting that they suggest a functional disturbance rather than an organic vascular lesion. However, the existence of such a cerebral vasospasm has never been proved. A long time ago, with other collaborators, we tried to demonstrate this;[8,9] recent investigations tend to confirm our original point of view.[10–12] The cerebral arteries, if indeed they are supplied by specific nerve fibers, do not react quantitatively as do other structures innervated by the autonomic system. Moreover, stimulation or section of the vegetative system does not provoke spasm. No chemical substance has such an effect. The caliber of the cerebral arteries can be varied by changes in arterial pressure and in the oxygen and carbon dioxide concentration in the blood, but these modifications are not identical with spasm. Spasm is brought about only by mechanical or electrical stimulation applied directly to the arterial wall. An embolism[13] may produce a spasm, but we cannot conclude that this is the characteristic reaction of the cerebral arteries in atherosclerosis. The situation is different in the internal carotid arteries, where vasomotor stability is determined by the vegetative nervous system. They may undergo spasm but its etiologic significance in production of transient cerebral attacks seen in atherosclerosis is highly questionable.

The mechanisms of transient cerebral attacks must be explained on the basis of known clinical and anatomic facts, namely, arterial occlusion and its immediate consequences, the sub-

sequent circulatory changes, and the role of the superimposed general circulatory disturbances.

For a long time, the most important cause of cerebral circulatory disturbances was concluded to be the occlusion of a cerebral artery. Its importance, however, was questioned some thirty years ago because of the frequent occurrence of cerebral softenings in the absence of intracranial arterial occlusion and, more recently, because arteriography demonstrated the high incidence of internal carotid artery occlusions.

The occlusion of an artery and the sudden interruption of its blood flow result in ischemia distal to the occlusion. This ischemia may be ephemeral as evidenced by transient clinical attacks, which leads us to believe that the arterial circulation is reestablished by anastomotic channels capable of insuring a good vicarious blood supply. This sometimes happens. But we must remember that, in addition to the main arterial cervicocranial supply, there is another arterial supply that does not intervene under ordinary conditions. It consists of an anastomotic network linking the external to the internal carotid arteries by means of the ophthalmic artery, the communicating arteries of the circle of Willis, and, finally, their distal branches formed by anastomoses on the surface of the cerebral cortex.[1,14,15] When a main arterial trunk is obstructed, this collateral system is called into play. Its functional potentialities depend, firstly, on the anatomic structure of the anastomoses, which varies greatly in different subjects; secondly, on the site of the obstruction in relation to this anastomotic network; and, thirdly, on the speed with which the arterial obstruction occurred. In fact, the value of the collateral supply is usually limited. Thus, if the integral carotid artery is occluded, all anastomotic vessels may be activated. Under these circumstances, a satisfactory vicarious blood supply may be established provided the obstruction has taken place slowly, permitting a progressive adaptation to the anastomoses. When this has happened and the obstruction is then abruptly completed by, for example, a hemorrhage in relation to an atheromatous plaque, sudden ischemia ensues but may be rapidly compensated and result in only a transitory cerebral attack.

It is significant that these transient clinical attacks are observed much more frequently with occlusions of the internal carotid artery than with those of the middle cerebral artery. In the latter case, the circulation can be reestablished only by superficial cortical anastomoses with limited functional capacity. The rare cases in which a silent occlusion of the internal carotid artery occurs prove that the collateral supply can adapt itself so well that occlusion of the vessel may occur without clinical manifestations.

Arterial narrowing or obstruction does not in itself afford a satisfactory explanation of these phenomena. While it may account for an attack, it does not explain recurrences. How can we understand these transient attacks recurring months or years before an arteriogram reveals a carotid or middle cerebral artery obstruction? How can we understand those fleeting attacks that occur months or years after arteriography has demonstrated an arterial obstruction while a normal nervous system offered convincing evidence of an adequate cerebral blood supply? This is the root of the problem.

Several hypotheses have been advanced to explain these transient attacks: progressive narrowing of the arterial lumen by a process of "fits and starts;" transient vasospasm of the affected artery or of the collateral vessels after a previous occlusion; or the discharge of emboli from an arterial lesion. All these concepts are hypothetical and, even if they are true, probably constitute exceptions rather than the rule.

It is probable that a general circulatory factor plays a determining part.[4,8,16] It has long been known that a sudden fall of the systemic arterial pressure may induce cerebral softening.[17–19] Normally, the cerebrovascular system is adapted to the arterial pressure, so that variations in the pressure within certain limits are compensated for and the blood flow remains normal. This no longer obtains in cases of obstructive lesions. The decrease in the arterial blood flow is considerably greater if the arterial lumen is narrowed and is even more marked in the accessory networks in which the arterial pressure is normally low. Thus, the cerebral circulatory dynamics are dependent on two essential factors: first, the

organization of an arterial network subject to atherosclerosis and to the development of anastomotic passages and, second, the functional state of the general circulation subject to variations of cardiac flow and systemic arterial pressure. Either a partial or a complete obstruction may be compensated for by anastomoses under normal circulatory conditions.

Even a slight fall of arterial pressure carries the risk of extensive reduction of blood flow in a narrowed artery and suppressed collateral supply. Neurologic symptoms then appear according to the degree of damage in the territory exposed to ischemia. If the fall of pressure is transient, a fleeting clinical attack ensues. It is easy to understand that such remittent attacks may arise and recur with variations of arterial pressure. This interpretation is not purely theoretic, for we have had occasion to verify it clinically. One of our patients[7] affected by bilateral occlusion of the carotid arteries had a transient attack associated in each instance with a fall in blood pressure. This mechanism may account for attacks that occur during the night with the patient at rest or after exertion.

The role of hypotension is also supported by the greater frequency with which these transient attacks are observed in cases of obstruction of the carotid artery as compared to those of the middle cerebral artery. In the former, conditions are such that the obstructive lesions may progress without giving rise to cerebral disturbances, but they are also such that the cerebral blood supply depends on the integrity of anastomotic channels, the functional value of which is particularly influenced by variations of the arterial pressure. This concept takes into full account the recurrence of the ischemic attacks in the same cerebral area with a blood supply that has been diminished by atherosclerotic lesions. Frequently, this same territory will later be destroyed as the result of a more severe attack. By considering both transient and definitive attacks together, it is easy to understand that the intensity and duration of the ischemia are the result of the combined action of anatomic and functional factors. This concept eliminates the mechanistic view, which demands the presence or absence of an arterial obstruction to explain cerebral ischemic attacks.

This is just a simplified outline. The structural alterations include more than atherosclerosis of the carotid artery and its branches, while there are functional factors involved in the condition other than the fall in blood pressure alone.

The structural alterations include all arterial lesions. Here we begin to see the place held by bilateral obstruction of the internal carotid arteries, which only a short time ago was considered incompatible with life. If symptoms and signs of obstruction of one internal carotid artery remain dormant, it is partly because the other carotid contributes to the vicarious supply.

An obstructive lesion of the second carotid artery increases the precarious state of the circulatory conditions and induces transitory or definitive ischemic accidents. This we have observed during the development of the illnesses in 2 of our 4 patients with bilateral internal carotid artery occlusion.[7] They had fleeting attacks of sudden and transient aggravations affecting in an irregular way a limb or half of the body. Such was the case of a 51-year-old man (ZU), who had left hemiparesis occurring intermittently over a few weeks. During the same period, he suffered from monoplegia lasting a few minutes, which involved the right arm on one occasion and the right leg on another.

Arteriographic study demonstrated bilateral occlusion of the internal carotid arteries at their origin. Similarly, in atherosclerosis of the vertebrobasilar system, obstruction may reveal already existing circulatory deficiencies of the carotid system. Perhaps the modifications that develop in the cortical arterioles[20] because of new hemodynamic conditions of the vicarious system play a part in the origin of certain ischemic attacks.

As for the functional modifications of the circulation, they are certainly not restricted to decreases in blood pressure and cardiac output. For instance, repeated transitory attacks within a few hours have been observed in bedridden patients whose arterial pressure and cardiac rhythm remained unchanged. When the blood pressure is lowered, it does not as a rule induce disturbances identical with the transitory attacks. In our patients affected by the most recurrent transient episodes without

arterial occlusion, carotid compression never produced these transitory attacks. In cases of unilateral obstruction of the carotid artery, the disturbances following arterial compression on the healthy side were very different from the typical ischemic attack; compression produced general discomfort and loss of consciousness, which is so rare in transient ischemic episodes. This is rather difficult to understand.

Ischemia is the common denominator of all transitory attacks, but, in the anatomic and functional evolution of atherosclerosis, the circulation probably undergoes disturbances of different types. In a general way, we would like to contrast isolated neurologic attacks remitting in one or several days with those which show very restricted involvement of the body, are very brief, and recur with astonishing frequency for several days. The former may result from an obstructive lesion and a fall in blood pressure. The latter possibly correspond to functional oscillations in the vascular networks in which vicarious blood supply has been established. The prodromic phase of migraine offers an example of a derangement at the arteriolocapillary level. Of course, it is not analagous to atherosclerosis, but functional disturbances might perhaps occur in an area where a new circulation has arisen. We know nothing of the dynamics of the cerebral circulation during a transient attack. Could it not be that focal disturbances of the intracerebral circulation are produced under the influence of tissue and intravascular factors that regulate the blood flow? Perhaps.

TREATMENT

At present, only a few general principles of treatment can be considered.

The transitory attacks being of ischemic origin, it would be logical to expect clinical improvement with the use of vasodilators. No true medical treatment is known to have any such action on the cerebral arteries. The use of peripheral vasodilators carries the risk of decreased blood pressure. Blocking of the cervical sympathetic ganglia is ineffective except that perhaps it increases the carotid blood flow. Inhalation of a gaseous mixture rich in carbon dioxide, which induces arterial vasodilation, does not improve local metabolic exchange.

Experimentally, only the inhalation of oxygen will retard the development of the biologic disturbances that follow ischemia[21] and, being devoid of danger, is well worth trying. It is obvious that the patient must also have complete rest and that the blood pressure be maintained at normal levels.

Indeed, it is rather toward the future that a therapeutic study must be directed. Transitory attacks must always be attended with the dread of a major stroke. If one is poorly equipped to deal with the general circulatory disturbances, one possesses perhaps in anticoagulant medication a method which in part combats the formation of a thrombus and which, in association with dietetic and appropriate regimen, may help to diminish the risk of cerebral softening. It is difficult to evaluate the results of trials with these treatments, but they give a favorable first impression.[22,23]

In the case of partial and recent obstruction of the carotid artery, what can be expected from surgical intervention designed to reestablish arterial continuity? The procedure is based on a sound principle, and the early results in transitory attacks are encouraging.[24,25] It is to be hoped that the difficulties which make this type of surgery exceptional will be overcome.

SUMMARY

Transitory ischemic attacks are frequently observed in the evolution of cerebral atherosclerosis. They manifest themselves by motor, sensory, or aphasic attacks of a few minutes' or hours' duration. They may be frequent or infrequent. They are observed at intervals of a few days to several years before the occurrence of cerebral softening. Rather than attribute them to a hypothetic cerebral vasospasm, it is advisable to regard them as the result of the combined action of atherosclerotic lesions and general disturbances of the circulation.

The underlying mechanisms of these attacks are, however, still not entirely clear. The transitory attacks are usually the expression of the onset of a circulatory insufficiency. It is perhaps possible at this stage to reduce the risks of this insufficiency for the future well-being of the patients.

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Congenital aphasia

A clinicopathologic study

William M. Landau, M.D., Robert Goldstein, Ph.D.
and Frank R. Kleffner, Ph.D.

CONGENITAL APHASIA has been recognized sporadically in the neurologic literature for well over half a century.[1-5] Several authors have been especially concerned with the labeling of the phenomenon, for the term aphasia is usually applied to a condition in which speech and language are affected after they develop normally. Since aphasia means absence of speech and since the child who loses normally acquired oral language and its understanding is often not behaviorally distinguishable from one with retarded language development,[6] we shall use the term congenital aphasia without apology.

These children are distinguished by a relatively isolated defect in the development of expressive and/or receptive aspects of oral language.[7,8] The lack of language is not primarily due to auditory insensitivity, emotional disturbances, or mental retardation.

The present case was examined during a neurologic survey of a school population of aphasic and deaf children.[9,10] No previous cases with pathologic study have been reported.

CLINICAL HISTORY

The white male subject was born in 1945, the product of an uneventful eight and one-half-month pregnancy and a five and one-half-hour labor. His only sibling, a female four years younger, has congenital maldevelopment of the musculotendinous structures in both legs. The mother also has had one spontaneous abortion after three months of gestation.

The boy was normal at birth but was subsequently noted to be cyanotic at the age of 10 days, when a cardiac murmur was also detected. He ate poorly and was always underweight. He had pneumonia at 3 months and again at 1, 2, and 3 years of age. Dorsal scoliosis developed during the first year of life. He sat at 14 months and did not walk until 5 years. However, he was toilet trained at 18 months.

In 1952, at age 6, the patient was studied at the Johns Hopkins Hospital Cardiac Clinic. He was observed then to be poorly nourished and poorly developed, with marked right scoliosis. It was noted that he had no speech, although he seemed quite bright. He was cyanotic and polycythemic; red blood cell count was 7,600,000, hemoglobin 20 gm., and hematocrit 53%. A precordial thrill and harsh systolic murmur were heard.

The cardiac tests were summarized: "All the cardiac studies indicated that there was a definite transposition of the great vessels. The facts that the pulmonary artery was catheterized from the apparent right ventricle, that the oxygen saturation of the pulmonary artery was higher than that of the femoral artery, and in turn, that the femoral artery was higher in saturation than the right ventricle, all were suggestive of a diagnosis of a Taussig-Bing syndrome, transposition complex. Supporting this diagnosis was the fact that cyanosis was present at birth, and in addition there was only mild cardiac enlargement with very large pulmonary arteries. That the child continues to do well so far as physical activity is concerned is also characteristic of the Taussig-Bing abnormality."

Early the same year, he was first seen at the Central Institute for the Deaf. Though he responded to a variety of sounds including

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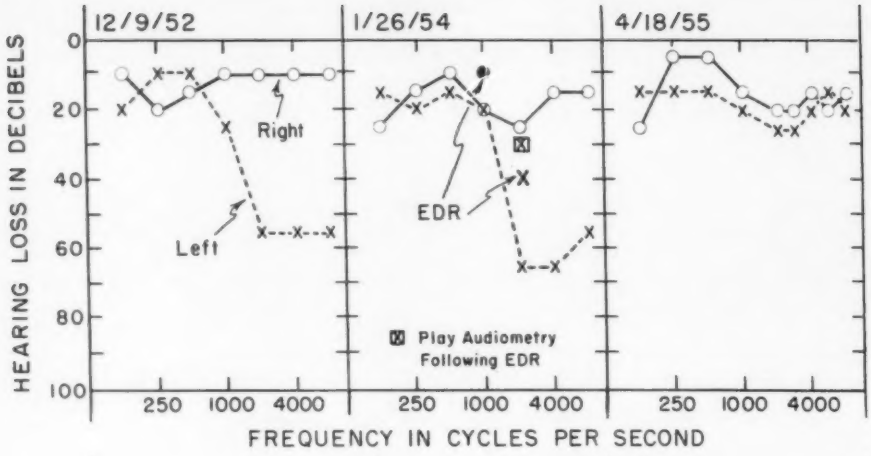

	Live Voice	Noise	Live Voice	Noise	4-C	Noise
RIGHT	5 db	5db	10db	10db	10db	15db
LEFT	5 db	5db	5db	5db	16db	15db
FIELD	10 db	10db	15 db	15 db	13db	15 db

Fig. 1. Serial audiograms. See text for details.

speech, it was quite apparent that he did not comprehend spoken language. He obviously reacted to low intensity sounds. Attempts to communicate consisted of facial expressions and gestures accompanied by vocalizations that varied appropriately in pitch, inflection, and volume with the meanings he seemed to be trying to convey and occasionally included appropriate single words. This vocal pattern, "scribble speech,"[7] was usually devoid of actual words (compare with "idioglossia" of Worster-Drought and Allen[4]). He could imitate short words well enough to show that he heard them, but it was evident that he did not know their meanings. His attempts to imitate phrases and sentences resembled the original only in rhythm and inflection. The pattern of "scribble speech" remained constant as he repeated the same sentence.

He matched colors readily but did not say their names or identify colors named by the examiner. When shown a picture of a thermometer he said "house" and gestured to show that there was one in his home. When he saw a picture of a hammer, he hit his hand on the desk and said, "Ah dah dis too."

During the entire examination, the child was friendly and outgoing and was willing to attempt everything requested. He appeared socially and intellectually alert. His primary deficiency seemed to be a lack of ability to comprehend spoken language, a defect accompanied by lack of speech. He scored an IQ of 78 on the Advanced Performance Scale,[11,12] although the psychometrist thought that the child's general behavior indicated at least normal intelligence.

Individual instruction by technics developed for aphasic children[7] was soon begun. He showed eager attention and concentration and demonstrated good ability to learn and retain new vocabulary. He began to use appropriately, though with poor articulation, occasional words and phrases heard in casual speech ("Let's see," "What's that?", "Mama wash"). However, the increase of language usage and

comprehension in the next months was confined to the materials formally taught.

He entered full time classes for aphasic children in September 1952, and the first test by behavioral pure-tone audiometry was attempted in December (Fig. 1). The right ear was tested first, and responses were fairly reliable. By the time the left ear was tested, the responses became more inconsistent. A repeat test on the right ear was entirely inconsistent. If these results are considered to be accurate, the subject's hearing was essentially normal, except for higher frequency tones in the left ear.

Speech audiometry with monitored live voice was also tried on the same day. The task was to identify familiar objects when their names were spoken (children, car, flower, baby, shoe, boat, and airplane). All of these words had previously been learned. His responses were quite consistent. With earphones, he showed a 5-db threshold hearing level (normal) in each ear and a 10-db level (normal) when the words came from the loudspeaker. He showed approximately the same threshold levels for white noise. Pure-tone audiometry attempted two days later was entirely unreliable. However, he again showed normal thresholds for noise.

On a repeat test of the Advanced Performance Scale in June 1953, he scored an IQ of 97. He had acquired a functional reading, writing, and speaking vocabulary of at least 175 words, which included nouns, adjectives of color, number, and size, gerunds, and a few verbs and prepositions. He knew numbers to 5, but his number concepts were poor. He had learned and could recite from memory simple 4- to 6-sentence descriptive stories and could use the learned sentences in answer to rote questions.

The next audiograms were made in January 1954 (Fig. 1). Responses in pure-tone audiometry were again inconsistent. With electrodermal audiometry, a 10-db threshold hearing level was obtained at 1,000 cps in the right ear and a 40-db threshold level for 2,000 cps in the left ear. Immediately after this test, the threshold level for 2,000 cps was found to be 30 db by play audiometry. Speech audiometry by monitored live voice again elicited the most reliable responses and indicated hearing levels within the normal range. Thresholds for white noise and speech were identical.

By the end of the second school year, he spoke in grammatically correct simple sentences. The quantity and flexibility of vocabularly and syntax that he used effectively were increased, and he could read and write both cursive script and printing. He could add and subtract accurately numbers up to 10. His capacity to learn from casual conversation was also increased.

In March 1955, the American School Achievement test showed an educational age of 7 years 3 months, with an educational quotient of 76 and a grade equivalent of 2.0. In April, his responses to pure-tone audiometry were again inconsistent (Fig. 1) but the more reliably determined speech thresholds were practically normal. No bone conduction measurements were made.

A neurologic examination was performed in May 1955. The patient was misshapen, wizened, slightly cyanotic, and physically underdeveloped for his age. Marked right kyphoscolosis was noted, and the precordial systolic thrill and murmur were apparent. Both carotid arteries in the neck pulsated well, and there was no cervical or cephalic bruit. The child was bright and sentient, and no hearing deficit was evident. He was right-handed and left-eyed. The optic fundi were normal, and the visual fields were normal to confrontation with a small white light target. Both eyes tended to move upward upon medial gaze. The palate was asymmetric, with slightly less elevation on the left. Touch, pain, vibration, and position responses were intact. Figure writing on the hands was reported accurately about half of the time. Double simultaneous touch stimuli to both hands, both sides of the face, or face and hand on the same side were perceived accurately without training. The gait was mildly diplegic, with slight flexion of the left upper extremity and stiffness at the left knee. He could walk on his toes and on his heels. The Romberg sign was absent. General muscle strength was good. Finger-nose and heel-knee tests were well performed bilaterally, as were rhythmic movements. He performed fine rapid movements of the fingers and symmetric. The plantar reflex was flexor on the left and extensor on the right.

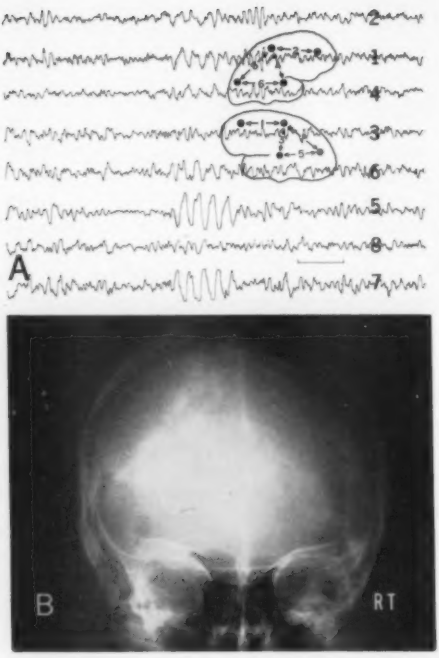

Fig. 2. [A] Electroencephalogram, bipolar recording as indicated. [B] Skull roentgenogram

The electroencephalogram showed slow dysrhythmia with left occipital focal trend (Fig. 2A). Skull roentgenograms showed an asymmetric vault with right parietal flattening (Fig. 2B).

A progress summary in June 1955 indicated successful comprehension and use of tenses, regular and irregular verbs, time phrases, partitives, and so forth, with a rapidly expanding vocabulary. His use of language was still best in the structured lessons, but spontaneous speech was effective even when less accurate. He comprehended oral language best when it was spoken slowly, with a definite pause after each word, and he failed to comprehend any but the most familiar expressions when spoken at a normal rate. (We believe that this is a feature characteristic of children we have classified as receptive aphasic.) He continued to be physically active in spite of his handicap and was socially happy, outgoing, and friendly.

In December 1955, at age 10, the child became ill with mumps and died suddenly, presumably because of a cardiac complication.

PATHOLOGIC STUDY

The autopsy was supervised by Dr. Sarah Luse, who subsequently kindly supplied us with all available tissue. The general pathologic diagnoses included:

- Congenital heart disease with [1] complete transposition of the great vessels, [2] interventricular septal defect (3 cm.) with overriding of the transposed pulmonary valve, [3] patent ductus arteriosus, [4] anterior noncoronary cusp of the aortic valve, [5] hypoplasia of the aorta, [6] hypertrophy of the pulmonary artery, [7] hypertrophy and dilation of the heart, [8] advanced pulmonary arteriosclerosis, and [9] clubbing of the digits of all extremities
- Scoliosis of the thoracic spine with prominence of the left anterior thoracic wall
- Congestion of the kidneys, left lobe of the liver, pancreas, spleen, small intestine, and bladder
- Focal atelectasis of the lungs
- Emphysema of the lungs, moderate
- Depigmented infarct of the middle lobe of the right lung
- Petechiae and ecchymoses of the thymus, small intestine, colon, and stomach
- Altered blood in the small intestine.

The brain weighed 1,150 gm., and external examination revealed no abnormality of the vessels at the base. The anterior portion of the cerebrum was of normal size and configuration. However, posteriorly, there was a bilateral loss of cortical substance starting from the inferior and posterior margin of the central sulci anteriorly and extending backwards along the course of the insulae and sylvian fissures toward the occipital lobes on each side. The area of loss on the right side was 6 cm. in length and about 2 cm. in width, the gap bridged by slightly thickened meninges. The similar area on the left had the same

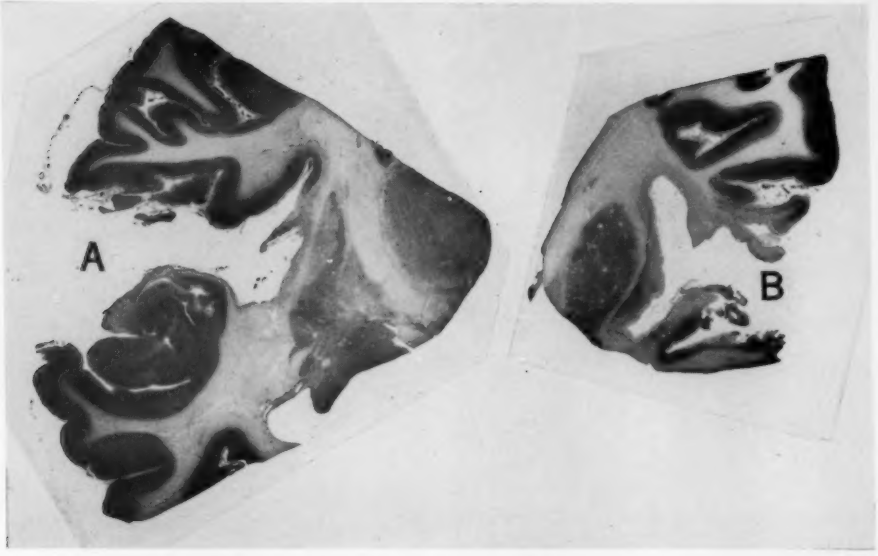

Fig. 3. Coronal sections through sylvian fissures showing gross degeneration of insulae and opercula. Nissl stain. [A] Left. [B] Right, farther anterior plane

width but extended 8 cm., almost to the occipital pole. The gyri of the posterior portion of the parietal, temporal, and occipital lobes bilaterally were reduced in size, and increased numbers of convolutions were present. Multiple step sections through the brain failed to reveal any abnormalities anterior to the central sulci, but, posterior to this region, there was atrophy of both white and gray matter of the insulae, their opercula, and the tissue immediately behind extending into the occipital lobes. No thrombi or other vascular lesions were found to account for these infarcts, although the distribution was that of the middle cerebral arteries. On the left side, the terminal 2 cm. of the lateral ventricle just medial to the infarcted area was obliterated. Brain stem, cerebellum, and spinal cord were grossly normal.

Microscopic sections cut coronally through the sylvian fissures showed gross degeneration of the insulae and opercula bilaterally (Fig. 3). In the brain stem, the normally distinct medial geniculate structures, closely related to the lateral geniculate nuclei and cerebral peduncles, were difficult to identify (Fig. 4). Although it is not possible to say that there was complete atrophy of the medial geniculate nuclei, it was obvious that they were severely degenerated. Both pyramidal tracts were degenerated along their ventral margin in the medulla (Fig. 5B). Both auditory nerves were histologicaly intact (Fig. 5A). The inner ear structures were not examined.

COMMENT

Many authors have observed that a lesion of either the right or left cerebral hemisphere in the infant or young child does not lead to aphasia. Bilateral lesions were therefore to be expected in the present case.

Our pathologic data are sufficient to show severe damage to the primary auditory projection pathway bilaterally, with corresponding retrograde degeneration of the medial geniculate nuclei. We cannot say whether a possible small amount of residual functional tissue in this system may account for the sub-

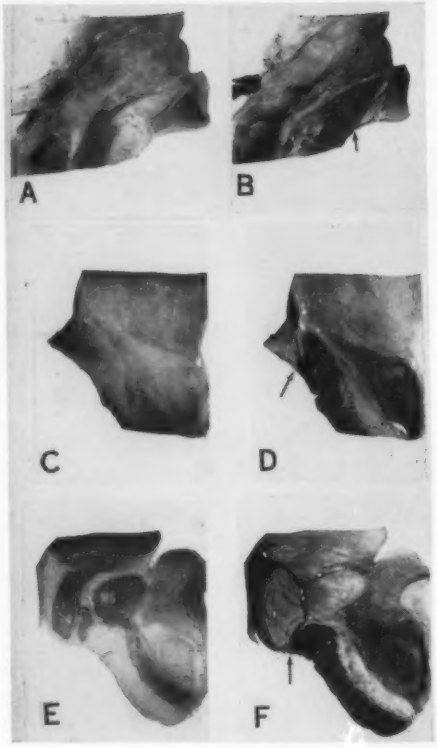

Fig. 4. Brain stem cross sections. Nissl stain in left column, Weil stain in right. [A and B] Level of posterior commissure, left side. [C and D] Section farther posterior, right side. [E and F] Normal brain stem from a 13-year-old child. Arrows indicate junction of cerebral peduncle and lateral geniculate nucleus, normally adjacent to medial geniculate nucleus (MG in E).

Fig. 5. [A] Pons. Veil stain. Normal appearing eighth nerves. The right nerve is complete in adjacent sections. [B] Medulla. Weil stain

ject's demonstrated capacity to develop speech and language. It seems more likely that the auditory, like other afferent systems,[13] has a functional sensory pathway in the brain stem and medial thalamus which is phylogenetically older than the laterally situated geniculate-cortical path; the old medial pathway may then be the essential neurologic substrate for language development in this child.

Against this hypothesis is the lack of evidence for conduction of auditory sensation by the medial pathway in the adult in whom bilateral hemispheral lesions have been reported to produce deafness,[14,15] but these reports lack modern audiometric tests and histologic study of the peripheral auditory apparatus. Further case studies may indicate only a quantitative difference in degree of compensatory function after equivalent lesions in infancy and in adult life.

The cerebral lesions in this case were not limited to the auditory system, and the clinical picture may be partially related to destruction of other structures in the sylvian region. Further, it would be gratuitous to infer that gross lesions of the geniculate-cortical system are likely to be found in most other cases of congenital aphasia, for a large portion of the congenital aphasic population shows no collateral clinical or laboratory evidence of such extensive lesions.[9,10]

The speech behavior of this boy was indistinguishable from that of other congenitally aphasic children; similar behavior also occurs

in children who acquire and transiently lose language, presumably because of seizure states affecting the sylvian areas.[6] We would emphasize that residual function is due to residual tissue; the lesion may be less constant than the adaptive mechanism that remains undamaged.

SUMMARY

Congenital aphasia occurred in a child who also had cyanotic congenital heart disease, which led to his death. His hearing and intelligence were within normal limits, and, with special instruction, he had acquired considerable useful language. Autopsy revealed bilateral old infarctions in the sylvian regions and severe retrograde degeneration in the medial geniculate nuclei. Language function therefore appears to have been subserved by pathways other than the primary auditory thalamocortical projection system.

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Pathologic findings in patients with "centrencephalic" electroencephalographic patterns

C. Ajmone Marsan, M.D., and W. R. Lewis, M.D.

THE BILATERAL, symmetric, and almost synchronous paroxysms of rhythmic 3-per-second wave-and-spike complexes, although not too common, are one of the most striking and typical patterns in clinical electroencephalography. As is the case for most normal and other abnormal electroencephalographic rhythms and patterns, we still are ignorant of the mechanism at the basis of the production of these complexes, and their anatomotopographic "origin" is still a matter of controversy among the different investigators.*

Several reasons may be advanced which do not solve but justify the mere existence of such a controversy: [1] difficulty of reproducing experimentally the same characteristic pattern in animals, [2] tendency to confuse the issue by including other rhythms morphologically similar but basically quite unrelated to the pattern under discussion, [3] excess of investigations primarily designed to invalidate existing hypotheses at the expense of constructive criticisms or of proposals and testing of alternative theories, and [4] scarcity of demonstrable pathologic changes in those cases in which the pattern under discussion appears with its typical manifestations.

In regard to the first reason, up to now little could be done. The few available experiments in animals,[1–8] including the classic one of Jasper and Droogleever-Fortuyn,[9] speak for themselves. More crucial results are needed before any of the advanced theories can be accepted without reservations and applied to man. Similarly unsatisfactory and controversial remain the findings obtained in the few instances of human investigation.[10–18]

Much could be done, on the other hand, in regard to the second limitation. It should be clear by now that the mere association of a spike with a slow wave and possibly even the rhythmic repetition of such an association per se do not carry with them the same functional significance as that of the clinical "petit mal" pattern. This has in fact ben recognized in clinical electroencephalography since the middle 1930s, when the term "petit mal variant" was coined. However, the criteria for classifying a discharge as "classical" or "variant" are still too elastic and subjective, as one can judge, for instance, in Gibbs' *Atlas*[19] by comparing plates considered typical of the two patterns (for example, plates 6 and 17 and 40, 41, and 54). As a result, misinterpretations of records are still numerous, but it is particularly in the experimental field that these misinterpretations are bound to arise when they could instead be avoided by the simple application of more rigid criteria.

It is undeniable that criticism of existing theories, particularly when based on experi-

*This electroencephalographic pattern, commonly called "petit mal," is referred to, in this paper, as "centrencephalic" in analogy to the term used by Penfield and Jasper[20] (pp. 27, 28, and 622) in their classification of clinical seizures. In fact, when sufficiently long in duration, this pattern is at times accompanied by "absence," and its presence in the record is almost pathognomonic of "idiopathic" (or centrencephalic[20]) epilepsy. For this reason, it will be difficult to separate the electrographic aspects of the problem from its clinical features and implications, or to ignore the latter, in the following discussion, this notwithstanding the fact that, as the title implies, the present paper is primarily interested in the physiopathogenetic mechanisms responsible for this characteristic electroencephalographic pattern and not in the particular form of epilepsy which often, but not always, accompanies it.

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mental evidence,[3,20,21,22] might serve some purpose; on the other hand, one wonders whether efforts directed toward more constructive aims would not be more useful and rewarding.

The lack of characteristic or systematically localized pathologic changes in patients with typical petit mal patterns in the electroencephalograms has been a commonly accepted fact. Almost total absence of both gross and microscopic changes has been reported in the past and is generally taken for granted, the attitude being one of "wait and hope in the future of histochemistry" to get a final answer. Yet it is our feeling that electrographic-pathologic correlations, even though rarely feasible, could provide some useful information. A good example in a field very close to the present one is provided by Jasper and his collaborators,[23,24] who, by means of a careful correlative analysis, reached the conclusion that localized frontoparasagittal, supplementary motor, and orbitofrontal lesions may show patterns often indistinguishable from, or highly suggestive of, petit mal epilepsy; whether in these cases one wants to accept Jasper's hypothesis of "secondary bilateral synchrony" is immaterial. His results have proven of good diagnostic application, as subsequent studies of other investigators have repeatedly confirmed.[25–28]

Related to the last of the above mentioned limitations are the two cases to be presented. These may be considered as simple electroencephalographic curiosities but, together with the other few reported in the literature, could lend themselves to interesting physiopathogenetic considerations.

Case 1. An 18-year-old white married female was admitted to the National Cancer Institute with a chief complaint of pain in the neck. Three and a half months after full-term delivery of a stillborn male, she underwent dilation and diagnostic curettage because of continued postpartum bleeding and subsequently had panhysterectomy for choriocarcinoma of the uterus. The admission took place six weeks later, when signs of pulmonary metastasis were found on chest roentgenograms. Two weeks before admission, she had noted severe suboccipital and posterior neck pain aggravated by movement, and, after a few days, recurrent nausea and vomiting and unsteadiness in gait developed.

No seizures or disturbances in consciousness were ever present during hospitalization, and the past history showed no evidence of either major or minor attacks, a fact subsequently confirmed by personal contacts with the parents. Neurologic examination revealed a clear sensorium without abnormal findings, except for transient diplopia and a questionable blurring of the disk margins bilaterally. Neck extension elicited severe pain. A chest film confirmed the presence of multiple bilateral pulmonary metastasis, while cervical spine and skull films showed no abnormalities.

An electroencephalographic examination performed on the second hospital day was interpreted as follows: The record shows a fairly well developed background activity consisting of 7- to 9-per-second waves, maximal bioccipitally with considerable spread anteriorly, where they are intermixed with faster rhythms. Throughout the record, there are numerous sporadic paroxysmal bursts of 3-per-second or slightly faster sharp waves or ill-formed wave-and-spike complexes, either isolated or lasting one to two seconds. These discharges are bilaterally synchronous, maximal bi-frontal, with minor shifting asymmetries in amplitude or in the development of the spike component of the discharge. With drowsiness, there is a generalized flattening and some shifting slow waves, maximal posteriorly, without focal or lateralizing character. Hyperventilation elicits some bursts of atypical 3-per-second wave-and-spike complexes and several other brief paroxysms of sharp activity. With photic stimulation, there is a fairly good bioccipital "driving" effect, slightly higher in amplitude on the left, and, in coincidence with some of the trains of flickering light, an activation of bilateral diffuse paroxysmal discharges is noted (Fig. 1).

The record was interpreted as definitely abnormal and suggestive of some subcortical, potentially epileptogenic disorder. No clear evidence of cortical lesions was found, but, in view of the clinical history and of the morphology of the epileptiform potentials, the possibility of brain stem involvement was mentioned.

Neck and suboccipital pain, nausea, and vomiting occurred frequently during the first days of hospitalization. In the early morning of the fourth day, she was found lying on the floor beside her bed in light coma. She responded poorly to painful stimuli and to calling of her name; corneal reflexes were absent, and pupils were fixed at 2 mm. bilaterally with no response to light. Bilateral ankle clonus without a Babinski response was found. After a few minutes, consciousness became more depressed and the respirations rose from 6 to 12 per minute, alternating with periods of apnea; conjugate deviation of the eyes to the right was noted. Later, the corneal reflexes returned and there was a slight divergent strabismus. She did not respond to command or name, only reacting with withdrawal to pinprick. Abdominal reflexes were absent, ankle clonus had disappeared, and an extensor plantar response on the left and an equivocal response on the right were elicited. It was felt that the patient had suffered a hemorrhage into a brain stem metastasis. About two hours

later, she went into a flaccid coma with sudden cessation of respiration. Hypothermia and artificial respiration were started, and the subject remained four days in profound coma before dying.

Gross examination of the brain revealed symmetric cerebral hemispheres. No evidence of tumor was seen on the cortical surface, but attached and limited to the inferior margin of the falx was a smooth, slightly lobulated, well defined mass of about 1 cm. in diameter. The lateral ventricles were slightly dilated, while the third and fourth ventricles were within normal limits. On the posterior superior margin of the right cerebellar hemisphere was a large hemorrhagic area about 2 cm. in diameter, with softening of the surrounding cortex over a total area of 3.5 by 5 cm. Some yellowish degenerative changes extended approximately 2 cm. anteriorly (Fig. 2). Microscopic examination of the cerebellar lesion and dural nodule confirmed their metastatic trophoblastic nature. The final diagnosis was "choriocarcinoma, metastatic to lung and brain; acute brain stem compression secondary to hemorrhage into a cerebellar metastasis."

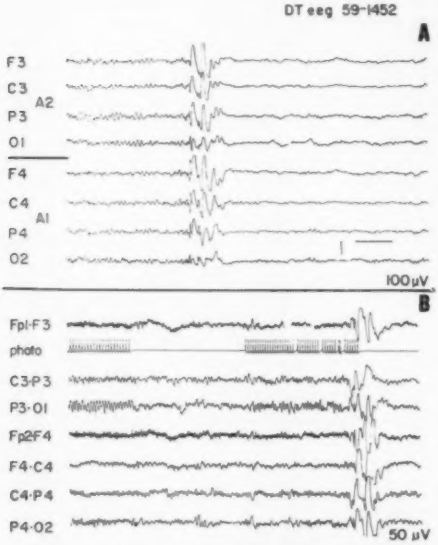

Fig. 1. *(Case 1)* Electroencephalographic samples. See text for details. [A] "Resting" record. [B] Photic stimulation. Time calibration: one second. In this and in Figure 5, the electrode placements are labeled according to the "10-20" electrode system of the International Federation.

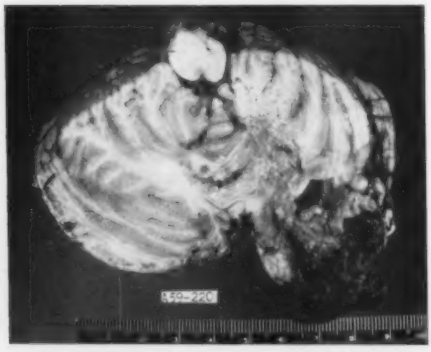

Fig. 2. *(Case 1)* Metastatic tumor of the cerebellar hemisphere

Case 2. An 8-year-old left-handed white male admitted to the National Institute of Neurological Diseases and Blindness had had seizures and speech and mental retardation since the age of 2.

The seizures were characterized by staring, flushing, circumoral pallor, pulling of the mouth to the left, slumping of the head, and, occasionally, falling with stiffening and clonic movements of all 4 extremities. During the past year, the parents had noted his occasional tendency to drag his left leg and to hold his left arm in an extended position. Skull roentgenograms performed before admission revealed calcifications in proximity to the tip of the right temporal lobe. Physical and, in particular, neurologic examinations appeared to be within normal limits; however, examination of the fundus revealed rather marked bilateral papilledema. On the basis of carotid arteriogram (Fig. 3) and an RISA brain scan positive for a right temporal lesion (Fig. 4), the diagnosis was made of right temporal lobe tumor extending deep toward the midline. Craniotomy was performed, and a cystic tumor within the right temporal lobe was almost entirely removed except for portions located mesially in the depth. No postoperative complications arose, but the patient continued to have occasional major seizures with falling to the floor and generalized symmetric jerking.

At the moment of this report, the final histologic diagnosis is not yet available; however, a smear made at the time of surgery revealed rather uniform cells representing astrocytes with increase of the fibrous elements. No mitoses and only a few multinuclear cells were seen, the tumor appearing grossly as a cystic astrocytoma.

A total of 6 electroencephalograms were obtained, three before and three after the operation. Samples of tracings from 2 different examinations in the postoperative period are shown in Figure 5. The preoperative tracings (1 of which was taken two years before the patient's admission) are all very similar and quite comparable to the postoperative ones. They show no clearly localizing

or lateralizing features, the most striking finding in all of them being the presence of high voltage paroxysmal spike-and-wave complexes at 3 per second or slightly less, at times typical and perfectly symmetric, at other times ill-formed or slightly different in amplitude (generally being depressed on the right). During an examination, simultaneously with the occurrence of these paroxysms, the patient had about 10 clinical seizures of brief duration which consisted of sudden extension and outward spread of both legs and arms, with the head and eyes turned slightly to the left.

Fig. 3. *(Case 2)* Right-sided carotid angiogram

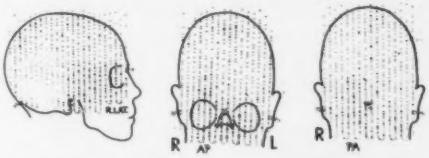

Fig. 4. *(Case 2)* Reconstruction of the RISA brain scan. Note that, in posteroanterior position of the head, right and left are reversed.

Thus, in summary, we have here 2 cases in which the electroencephalogram shows an almost typical and, in any case, highly suggestive pattern of "petit mal" epilepsy in 1 patient with a large metastatic cerebellar lesion but no clinical evidence of seizures and in 1 epileptic patient with petit mal, questionable "temporal lobe" episodes, and generalized convulsions, and a large astrocytoma that could be demonstrated deep within the right temporal lobe with extension toward the right thalamus.

In our limited personal experience, such associations are exceptional, and, also, judging from the available literature,[29–38] similar cases are seldom, if ever, mentioned (Table 1). In fact, their rarity makes the present as well as the previously published findings something of a curiosity; one could raise the question, as others[39–41] have done in the past, of a simple coincidental association of two unrelated disorders in the same subject.

To test this possibility, let us consider the figures in Table 2 where the incidence of brain tumors associated with 3-per-second wave-and-spike complexes is calculated with the assumption that the two phenomena are completely independent of each other. The results—based rather liberally on figures reported by various authors[42–46]—are obtained by multiplying their respective incidence in the general population. They show that, if chance alone were operating, we would expect such an association in 48.2 of 1,000,000 cases. With these figures, we can then set up a so-called theoretic or expected incidence or frequency of occurrence of 3-per-second wave-and-spike complexes in any sample of brain tumor groups, always assuming a purely chance relationship. Unfortunately, most of the available studies of electroencephalograms in brain tumors, while generally emphasizing or discussing the localization value of the method, do not provide details on the various electrographic patterns encountered.*

The few we could find to provide such information, at least as far as the occurrence of 3-per-second wave-and-spikes is concerned, are the 3 series[29,32,34] seen in Table 1. In these, which include a total of 1,071 brain tumors, our expected frequency of cases *with* 3-per-second wave-and-spikes would be 0.0517 case,

*It is worth mentioning here the findings of Lund.[47] In his very complete and detailed study, this author investigates the problem of epilepsy in brain tumors. Of 966 patients with intracranial neoplasms, 329 (or 34.1%) had seizures. No electroencephalographic examination was carried out, but the various seizure patterns were analyzed in detail and 36 patients (or 3.7%) were classified as having typical "petit mal" epilepsy. It is of interest that, in three-fourths of these, the tumor localization was as follows: 4 gliomas of the third ventricle; 2 diffuse, subcortical gliomas; 12 tumors of the frontal lobe with chief involvement of posterior-mesial portions of the lobe and, in half of these, of the corpus callosum; and 9 tumors of the temporal lobe with maximal involvement of "mesial and basal parts or extending deeply into the subcortical matter."

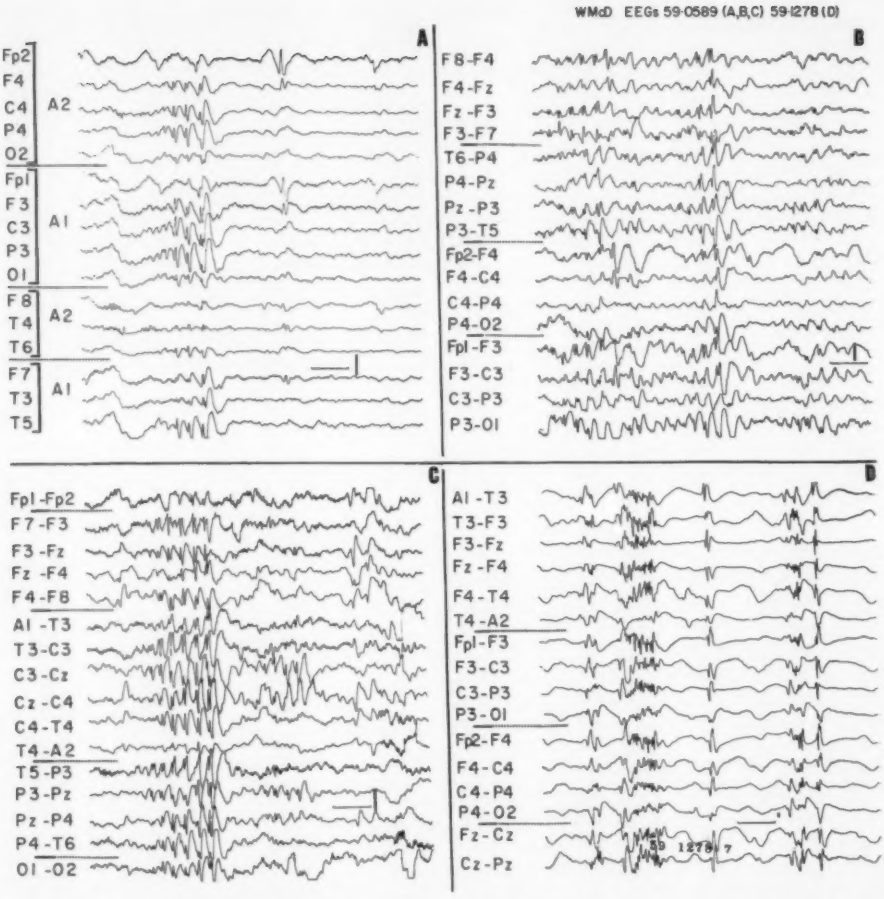

Fig. 5. *(Case 2)* Electroencephalographic samples from 2 postoperative tracings. [A, B, and C] Waking record. [D] Sleep record. Calibrations: one second and 100 μv. See text for description.

and, by subtraction, the expected frequency of cases in the same series *without* this particular electroencephalographic pattern would be 1,070.94 cases. The obtained or actual frequencies are, instead, 6 with and 1,065 without 3-per-second wave-and-spikes. By comparing expected and obtained figures and by testing the significance of their discrepancy, we obtain a χ^2 of about 600. This is such a tremendously high value that no table includes it; a χ^2 of about 6 would mean that the discrepancy could not have arisen by chance any more than 1 in 100 times. By a not too unrealistic guess, a χ^2 of 600 means that the discrepancy could have been due to chance only in about 1 in 100,000,000 times, which is to say that the probability that brain tumors and 3-per-second wave-and-spikes occur together in the general population *only by chance* is microscopically small. We can therefore conclude that, even though such an association is actually rare, it does happen far

TABLE 1. Cases of Brain Tumors Associated with 3-per-second Wave-and-Spike Complexes

Authors	*Year*	*Series*	*Number of cases*	*Lesion*		*Seizures*	*Comments*
				Nature	*Localization*		
Hoefer and associates[29]	1947	595 brain tumors	3	"Cyst"	Cerebellar, midline	+	Clinical "petit mal"
				Ependimoma	Fourth ventricle	+	Clinical "petit mal"
				Neurinoma	Acoustic nerve	+	Clinical "grand mal"
Bagchi and Bassett[30,32]	1950, 1953	400 brain tumors	2	Astro-cytoma	Cerebellar, hemisphere	−	Involving superior vermis
				Ganglio-glioma	Temporal	+	Clinical "petit mal"
Feld and associates[33]	1950	Isolated	1	Spongio-blastoma	Thalamus and interventricular	+	Clinical absences and grand mal (tuberous sclerosis)
Cuneo and Rand[34]	1952	76 brain tumors* (children)	1	Teratoma	Pineal	+	2 cm. in diameter; anterior and superior to vermis on superior pons surface; bulging into posterior portion of third ventricle
Moeller and Riegger[35]	1952	Isolated	1	Chief-cell, malignant	Posterior lobe hypophysis and hypothalamus	?	Discharges at 4 per second
Li and associates[36]	1952	Isolated	1	Malignant glioma	Hemispheral	?	Maximal frontoparietal and basal nuclear structures involvement
Fischgold and associates[37]	1954	Isolated	1	Angioblastic meningioma	Temporal	+	With "zone of softening" extending to retrolenticular part of internal capsule
Maccagnani and Riccio[38]	1959	Isolated	1	Ependymoma	Third ventricle	+	Clinical "massive flexor spasms"
Present series	1960	Isolated	2	Metastasis	Cerebellar, hemisphere	−	Also 1 small nodule on falx
				Cystic astro-cytoma	Temporal	+	Clinical "absences," automatism, and general convulsions (maximal involvement of basal nuclear structures and thalamus)

*Electroencephalographic study only in few subjects

TABLE 2. Incidence of Brain Tumors and 3-per-second Wave-and-Spike Complexes

Incidence	
Brain tumors (0.025–0.077* to 1.9%†)	0.019
"Epilepsy" (0.307 to 0.45%*)	0.00375
3-per-second wave-and-spikes in epileptic patients (13–15‡ to 18%§)	0.15
3-per-second wave-and-spikes in nonepileptic patients§	0.00197
Epileptic patients with 3-per-second wave-and-spikes in general population	56.2 in 100,000
Total cases with 3-per-second wave-and-spikes in general population	254.2 in 100,000
Chances of brain tumors associated with 3-per-second wave-and-spikes‖	48.2 in 1,000,000

*From Kurland[42,43]
†Average from various figures in Zülch[44] (verified hospital admissions and autopsies)
‡From Penfield and Jasper[46]
§From Gibbs, Gibbs, and Lennox[45]
‖If both are assumed to be independent of each other

more often than chance would permit, thus indicating that the two phenomena are indeed related.

From Table 1, the large predominance of subtentorial or midline localizations is rather suggestive, particularly if one considers that, of the few tumors in the cerebral cortex, at least two also clearly involved, if not maximally, basal nuclear structures and thalamus. This fact not only contributes to making improbable a purely coincidental association of the two phenomena but would, in addition, tend to deemphasize the role of the cerebral cortex and emphasize the role of midline, brain stem structures in the mechanism of production of 3-per-second spike-and-waves, which we like to label as "centrencephalic pattern." *

It is obviously unjustified to speculate on physiopathogenetic mechanisms on the basis of a few, sporadic cases in which, notwithstanding the demonstration of the main pathologic changes, other factors may indirectly account for the electrographic picture. On the other hand, in the last few years, evidence has accumulated showing that the incidence of truly idiopathic or genetic epilepsy is smaller than formerly believed. Traumas at birth[50] or in early or later life,[51–53] encephalitis,[54–58] and various organic processes[59–68] have been reported more and more often in the histories of patients with typical clinical and/or typical electroencephalographic picture of petit mal.

Hughlings Jackson, as quoted by Lund,[47] stated that "before we speak confidently of the causation . . . of cases of epilepsy without a known morbid anatomy, we should discipline ourselves by a study of cases in which necroscopy is likely to confront us." In analogy, it is safe to state that, if all the cases in which objective pathologic changes are available were carefully analyzed and reported, we could gain a deeper insight into the origin of this very characteristic yet still rather mysterious electroencephalographic pattern.

SUMMARY

1. The reasons for disagreement and controversial interpretations related to pathogenesis and anatomotopographic "origin" of the bilaterally synchronous 3-per-second wave-and-spike complexes are outlined and briefly discussed.

2. Clinical, pathologic, and electrographic findings in two patients are presented. In both, the electroencephalogram shows an almost typical and, in any case, highly suggestive pattern of "petit mal" epilepsy; one patient had a large metastasis of one cerebellar hemisphere but no clinical evidence of seizures, and the other had petit mal, temporal lobe episodes, and generalized convulsions, together with a large astrocytoma demonstrated within the right temporal lobe extending deeply toward the thalamus.

3. All similar cases of brain tumors associated with bilateral 3-per-second wave-and-spike complexes reported in the literature are reviewed. They are so rare that the question of a coincidental association of 2 unrelated phenomena might be raised; however, statistical evaluation shows that, if chance alone were operating, one would expect such an association in 48.2 of 1,000,000 cases. Thus, in 3 published reports of cases totaling 1,071 brain tumors, the "expected" frequency of cases with 3-per-second wave-and-spikes would be 0.0517 case, while the actual, "obtained" frequency is 6 cases. This discrepancy is highly significant ($\chi^2=600$), and one can safely conclude that the two phenomena are indeed related.

4. The large predominance of subtentorial or midline localizations in tumors accompanied by this characteristic electroencephalographic pattern is suggestive of a primary brain stem role in the mechanism of production of the pattern itself.

*Rather pertinent to the present study appear those of Boudin, Barbizet, and Labet[48] and Hann.[49] The former authors describe a case of "epilepsy of subcortical origin" with a tracing typical of petit mal, associated with endocrinopathy of diencephalic origin. In their survey of the literature, they find 22 similar cases of which, however, only 2 have pathologic findings (tuberculous lesion of the diencephalon and diencephalic gliosis) and only 5 have a complete electroencephalographic study. Hann describes a case of petit mal seizures in an 8-year-old boy with precocious puberty of hypothalamic origin (astrocytoma). His tracing was characterized by atypical spike-and-wave paroxysms.

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Functional decerebration in the cat

Comparative evaluation of cerebral ischemia and ultrasonic midbrain transection

Herbert L. Borison, Ph.D., Wesley G. Clark, M.S.
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THIS STUDY was prompted by the need in our laboratory for a chronic, functionally decerebrate preparation to be used in neuropharmacologic research. Our particular goal was to interrupt all impulse traffic through the midbrain without disturbing vascular and cerebrospinal fluid channels in the cranium. The anemic decerebration technic of Pollock and Davis[1] was the first to suggest itself. However, it appeared from published experience that the method was useful only for acute experiments.[2–4] Moreover, the fact that it had not been generally accepted as a laboratory procedure suggested that it should be reevaluated. The first series of experiments reported herein is concerned with the anemic decerebration technic; this method proved to be unsatisfactory for our purposes.

Our second series of experiments was concerned with ultrasonic transection of the midbrain. Fry and Fry[5] have coined the term "neurosonicsurgery" to describe the use of ultrasound for making circumscribed lesions in the central nervous system. The complex instrumentation required for irradiation with focused ultrasound, as described by Fry and Fry, makes their approach impractical for popular application in the experimental laboratory. Lindstrom[6] has developed a much less complicated technic of ultrasonic irradiation which utilizes a nonfocused beam delivered by a portable generator. We have successfully adapted this method for routine "bloodless" decerebration of the cat.

METHODS

All experiments were performed on cats. Pentobarbital sodium (35 mg. per kilogram) was given intraperitoneally whenever prolonged anesthesia was required. Ether was used as the anesthetic for short operations as well as for purposes of determining the prompt effects of certain procedures. Chronic surgery was carried out aseptically.

Anemic decerebration was attempted in 35 cats. A first-stage operation for ligating the basilar artery was performed in some of the animals a few days in advance of the main acute experiment. In most cases, however, complete procedures for producing cerebral ischemia were done in acute experiments as described later. Pollock and Davis[1] approached the basilar artery through the roof of the mouth. This operation seemed unnecessarily awkward; we regularly exposed the basilar artery by retracting the pharynx laterally after tracheal intubation. Figure 1 shows the excellent exposure of the basilar artery obtained by this approach. The artery was ligated with a silk thread passed under it with the aid of a fine curved forceps.

Ultrasonic decerebration was attempted in 55 cats. Our ultrasound generator (manufactured by F. Niesemann Co., Pittsburgh) energizes a plane wave applicator with an effective radiating surface of 7 sq. cm. and provides a sound beam at a fixed frequency of 1 megacycle per second at a variable power output of 1 to 10 watts per square centimeter in steps of 1 watt. Sound energy was delivered

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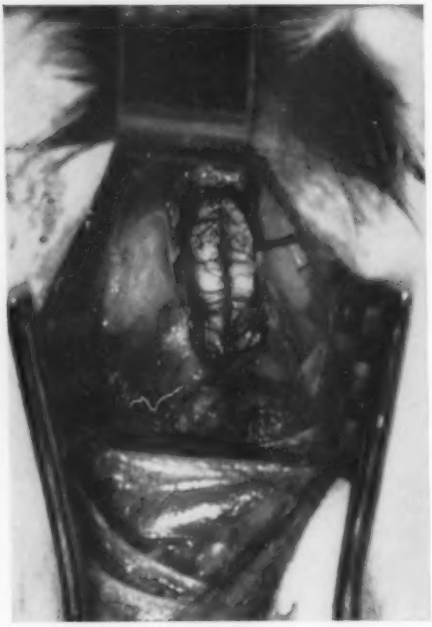


Fig. 1. Exposure of the basilar artery, from the foramen magnum to the sella turcica, by the parapharyngeal route. Note the tympanic bullae on either side of the ventral craniotomy.

to the brain through a Lucite cone, 2 in. deep and ½ in. in diameter at the openings, placed in contact with the dura mater. Degassed physiologic saline solution (boiled for ten minutes) was circulated through the cone at body temperature. This technic has been described for clinical use by Lindstrom and his associates[6,7] and was adapted by us for use in the cat. The experimental setup is shown in Figure 2. The soundhead was affixed to a standard sterotaxic instrument by means of an adjustable collar. Geometric coordinates for irradiation were decided upon from inspection of a cat skull and by means of the data in the atlas of Jasper and Ajmone-Marsan.[8] Approximately ½ liter of saline solution was required for cooling and for coupling the soundhead to the dura for each minute of irradiation. A ¾-in. parietal craniotomy provided a sufficient opening to allow unimpeded positioning of the cone on the dural surface. Bilateral craniotomy was performed for 2-beam irradiation. For purposes of 4-beam irradiation, the craniotomy was enlarged so as to form a slot across the cerebral hemispheres, thereby permitting stepwise movement of the cone from one side to the other. It was important to exercise great care to avoid excessive pressure of the cone on the brain, yet at the same time to prevent leakage of fluid around the edge of the cone. We found that contact pressure could be minimized by raising the abdomen of the cat, thus mildly elevating central venous and cerebrospinal fluid pressures. This maneuver caused the dura to balloon out slightly, thus providing a smooth, spherical surface against which to apply the cone. Only a few centimeters of water height were required to maintain adequate saline flow through the

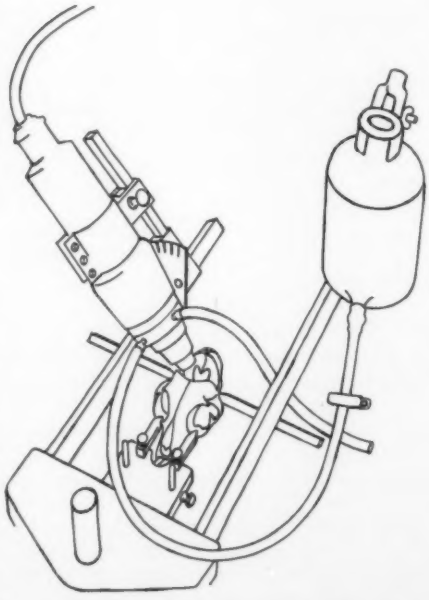


Fig. 2. Stereotaxic arrangement of soundhead, Lucite cone, and perfusing system for ultrasonic irradiation of the midbrain. The craniotomy has been purposely enlarged to show the geometric relationship of the cone to the bony tentorium.

cone; this was also controlled by adjusting the siphoning pressure through the outlet tubing.

A number of cats were prepared chronically with an indwelling cannula in the lateral cerebral ventricle, according to the method described by Feldberg and Sherwood.[9] Injection of 0.25 cc. of 1% methylene blue solution through the cannula, after ultrasonic midbrain transection, served as a means for assessing the patency of the aqueduct of Sylvius.

In some of the experiments on ultrasonic decerebration, blood pressure and respiration were recorded with appropriate transducers on a Sanborn Poly-Viso. The hypothalamus was stimulated with square-wave impulses from a Grass Stimulator through a bipolar electrode, oriented stereotactically, for the purpose of evoking responses that traverse pathways through the midbrain.

Rectal temperature was regularly observed. Brain specimens were perfused in situ with formalin and processed histologically. Only those specimens obtained promptly at time of death were considered useful for experimental evaluation.

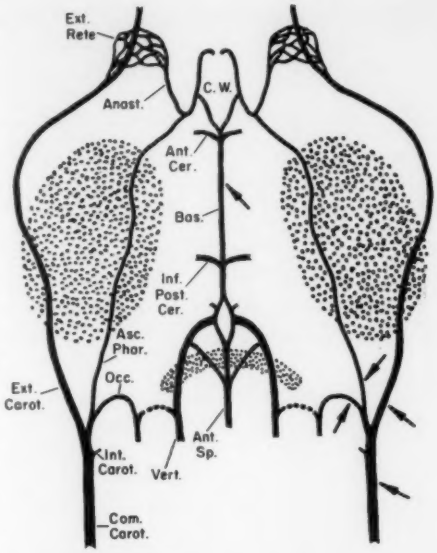


Fig. 3. Diagram of the carotid and basilar arterial distribution in the cat. Dotted regions represent tympanic bullae and foramen magnum. The interrupted line represents the occipital-vertebral anastomosis that is responsible for residual cerebral blood flow after occlusion of the common carotid and basilar arteries. The arrows indicate the points of ligation for producing effective cerebral ischemia.

RESULTS

Anemic decerebration. In all, 3 types of circulatory interference were used in the attempt to produce lasting decerebration. The first step of each procedure consisted in ligating the basilar artery above the origin of the inferior posterior cerebellar artery, as described under methods and illustrated in Figure 3.

Permanent occlusion of the common carotid arteries. This procedure was done in 5 cats. Ether anesthesia was maintained only until the carotids were ligated. Decerebrate rigidity developed at once but was not long sustained. The pupils became unresponsive to light within a few minutes. Brain stem reflexes remained brisk. During the next one or more hours, recovery slowly ensued and variable improvement, from head righting and vocalization to walking and alert behavior, became manifest. Nevertheless, the neurologic status of these animals ultimately deteriorated, and death due to respiratory failure occurred in two and one-half to seventeen hours after occlusion. In 2 cats, the external carotids were ligated instead of the common carotids. No difference in overall effect was observed, and the cats died after three and seventeen hours.

The following facts make it evident that basilar artery ligation and occlusion of the common (or external) carotids did not cause complete cerebral circulatory arrest: [1] partial recovery occurred despite permanent ligation of these blood vessels, and [2] head muscles remained active, thereby demonstrating adequate muscular blood flow that could supply the cerebral circulation through the external rete and anastomotic artery.[10]

Temporary occlusion of the common carotid arteries. Because of the possibility that permanent ligation might be responsible for delayed death, circulation was restored after varying periods of common carotid occlusion. In 2 cats, the carotids were occluded for thirty

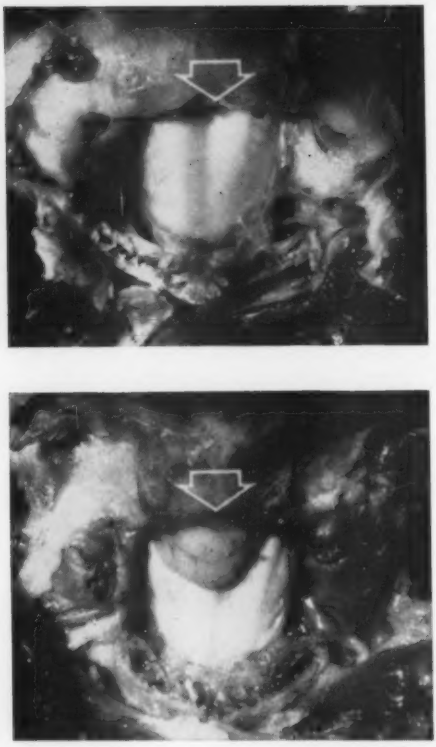


Fig. 4. Comparison of foramen magnum of normal cat (top) with that of cat subjected to anemic decerebration (bottom). Note extrusion of cerebellum as a result of brain edema in bottom panel.

minutes. Although both cats showed classic decerebrate rigidity during the period of occlusion, they recovered completely after the arteries were unclamped. Another cat had its carotids clamped for one hour and, although it went through a phase of partial neurologic recovery after circulatory restitution, death followed in the next twenty-four hours. In 1 cat, circulation was restored after four hours of occlusion. This animal rapidly deteriorated after removal of the clamps and died after forty minutes, as a result of brain stem depression, without passing through a recovery phase.

The main conclusions that may be drawn from these results are [1] recovery of cerebral function occurred after thirty minutes of circulatory occlusion even though decerebrate rigidity was evident during the entire period of ischemia and [2] restoration of cerebral circulation after partial ischemia for longer than one hour did not reverse the lethal process initiated by cerebral hypoxia.

Temporary occlusion of branches of the carotid bifurcation. It is clear that persisting decerebrate rigidity cannot be produced either by temporary or permanent occlusion of the common or external carotid arteries (performed in addition to basilar artery ligation). This may be explained by the residual blood flow through branches of the carotid bifurcation (Fig. 3). Accordingly, a more complete cerebral ischemia was attempted in the following manner. In the first-stage operation, in addition to ligation of the basilar artery, a mass ligature was tied around the medial limb of the carotid bifurcation, which includes the internal carotid (usually nonpatent in the cat), the occipital, and the ascending pharyngeal arteries.[11] This initial procedure produced no discernible neurologic deficit. The second stage consisted simply in occluding either the common or external carotid arteries for different periods of time. In contrast to the occlusion procedures described earlier, carotid branch ligation resulted in pupillary dilation, facial paralysis, tongue cyanosis, and early respiratory complications, as well as decerebrate rigidity. The more complete ischemia produced by this method caused more profound effects after shorter periods of occlusion. In 1 cat, complete recovery occurred after ten minutes of occlusion despite a transitory need for artificial respiration. Of 5 cats in which circulation was interrupted for fifteen minutes, 2 survived with partial recovery of cerebral function while the remaining 3 showed sustained decerebrate rigidity; these 3 died after periods varying from one and one-half to five hours.

Of 6 cats in which circulation was interrupted for thirty minutes, 4 showed classic signs of decerebration but died in from one to five hours, and 1 survived for twelve hours and made attempts to right itself; in the remaining cat, decerebrate rigidity was maintained for twenty-four hours before death supervened. It should be emphasized that, although brain

stem reflexes became obtunded and respiratory assistance was often required during the time of circulatory arrest, prompt recovery of brain stem function occurred after restoration of circulation. Unfortunately, early spontaneous death resulted in every case in which the decerebrate state persisted after cerebral circulation had been restored.

Cause of death after cerebral ischemia. In Figure 4, the foramen magnum of a normal cat is shown for comparison with that of a cat which died after temporary occlusion of the cerebral circulation. The development of brain edema, with consequent extrusion of the cerebellum and medullary bulb through the foramen magnum, is undoubtedly responsible for the delayed death that results from cerebral ischemia. In almost every case in which prompt postmortem examination was performed, protrusion of the cerebellum clearly was evident. Indeed, cerebral edema frequently made in situ perfusion of the brain with formalin impossible, owing to excessive intracranial pressure. Histologic examination of the cerebral cortex revealed the presence of extraneuronal edema. The pathologic findings agreed with the nature of the lethal process, which was characterized by progressive obtundation of brain stem reflexes and descending depression of the respiration manifested by successive apneustic and gasping phases. Such "decapitate" animals were kept alive by means of artificial ventilation for more than twenty-four hours without change in neurologic status.

Thus, it is apparent that, despite complete restoration of circulation after periods of ischemia sufficient to cause impairment of cerebral function, delayed death resulted from the development of brain edema. Furthermore, the onset of edema generally occurred more promptly after temporary, but relatively complete, occlusion than after permanent, but only partial, occlusion of the cerebral circulation.

Dye distribution during cerebral ischemia. Methylene blue (10 cc., 1% solution) was injected intravenously and permitted to circulate for different periods of time in cats with various kinds of circulatory occlusion. It was found that distribution of dye depended on the time permitted for circulation as well as on the type of vascular ligation. When the methylene blue was allowed to circulate for twenty minutes in a cat in which basilar and common carotids were tied, both forebrain and hindbrain were stained and only slight differentiation was evident between the two. By contrast, when the dye was allowed to circulate for twenty minutes after ligation of the basilar artery and the branches of the carotid bifurcation, the hindbrain was deeply stained while the forebrain remained essentially unstained, which is in keeping with the functional results of more complete cerebral ischemia produced by this type of ligation. On the other hand, in a cat in which only basilar and external carotids were tied (thereby sparing the occipital and ascending pharyngeal arteries), circulation of methylene blue for ten minutes still resulted in a clear-cut differentiation of dye in forebrain and hindbrain (Fig. 5).

Thus, it might falsely appear on the basis of dye distribution that basilar and external carotid artery occlusion provides as complete ischemia as does occlusion of all branches of the carotid bifurcation combined with basilar artery ligation.

Ultrasonic decerebration. *Effects of graded radiation exposure.* The effect of a single unfocused ultrasound beam (5 watts per square centimeter for sixty seconds) on the midbrain

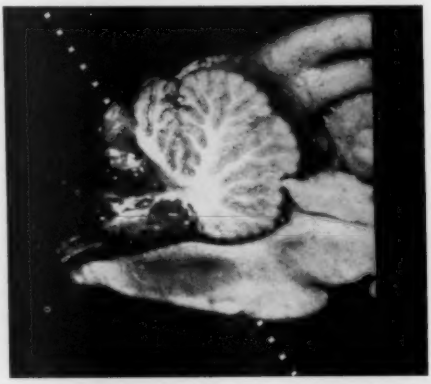


Fig. 5. Differentiation of dye distribution in lower brain stem after ligation of basilar and external carotid arteries despite the fact that blood was being supplied to the forebrain through the ascending pharyngeal artery. Dotted line coincides with upper boundary of deeply stained tissue.

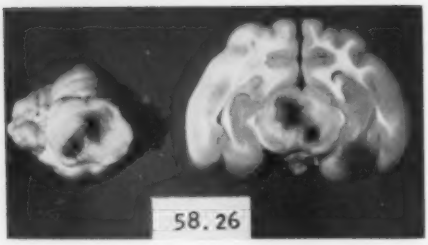


Fig. 6. Perfused specimen obtained twenty-four hours after midbrain exposure to a single beam of ultrasound at 5 watts per square centimeter for sixty seconds

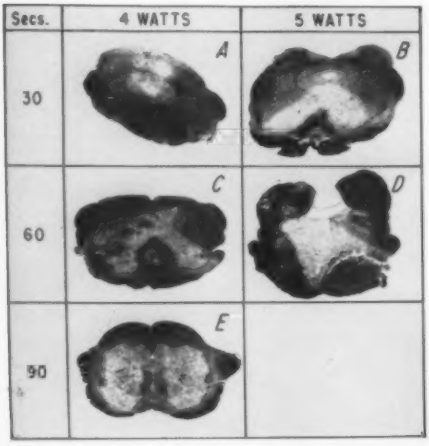


Fig. 7. Variety of lesions (areas of demyelinization) in the midbrain produced by ultrasound. Tissue sectioned at 10 μ and stained by Weil method. [A] 4 watts per square centimeter for thirty seconds was effective only in causing slight dorsal damage. [B] 5 watts per square centimeter for thirty seconds and [C] 4 watts per square centimeter for sixty seconds appear to be equally effective. However, 2-beam crossfire technic caused damage to trigeminal root. [D] Single-beam irradiation at 5 watts per square centimeter for sixty seconds caused excessive damage at base. [E] Parasagittal 2-beam irradiation at 4 watts per square centimeter for ninety seconds caused adequate damage, yet spared aqueduct and trigeminal nerve.

is shown in Figure 6. It should be noted that [1] the lesion is sharply demarcated by a band of necrosis which is restricted to the path of the beam, [2] no detectable damage resulted in the cerebrum overlying the midbrain, and [3] the temporal pole was damaged as a result of bone reflection of the ultrasound. While it was evident that this radiation dose represented a sufficient exposure for effecting a circumscribed lesion in the midbrain, further work was needed to determine the relationship between morphologic alteration of the tissue and impairment of function, as well as to establish a geometric coordinate scheme for producing complete transection of the midbrain.

Figure 7 shows a variety of lesions that resulted from exposures to beam intensities of 4 and 5 watts per square centimeter for periods of thirty to ninety seconds. Since a single-beam dose through the ½-in. coupling cone did not produce sufficient damage to make a fully decerebrate preparation, we used 2-beam and 4-beam sequences for more complete midbrain transection. Ultrasound intensity of 3 watts per square centimeter, even up to one hundred-twenty seconds in duration, was too weak to yield consistent lesions; moreover, damage often occurred too superficially, that is, within the overlying cerebrum. At 5 watts per square centimeter, lesions were produced with certainty after exposure for periods as short as thirty seconds, but, at this intensity level, difficulty was encountered from bone reflection with consequent spread of sound energy and excessive destruction at the base of the brain. As a result, an intensity of 4 watts per square centimeter was selected as the standard dose level; with this intensity, it was necessary to irradiate for at least sixty seconds at each exposure. The gross morphologic effect of applying a 4-beam sequence of 4 watts per square centimeter for ninety seconds in each position is shown in Figure 8. The geometric coordinates used to produce this lesion are shown in Figure 9.

The decerebrate preparation. Functional impairment after midbrain irradiation generally correlated well with gross tissue destruction caused by ultrasound. Thus, a necrotic lesion could be seen with the unaided eye in the brain of every cat which displayed neurologic

dysfunction and, obversely, a lesion was not evident grossly in those cats which appeared to be normal after ineffective ultrasonic irradiation. Accordingly, we could not expect to produce complete decerebration by using a single beam, even if sufficiently wide, without obliterating the aqueduct of Sylvius. Furthermore, since this type of irradiation yielded a cylindric lesion, it was advantageous to use multiple narrow beams spaced across the midbrain so as to minimize the rostrocaudal extent of destruction as well as to avoid obliteration of the aqueduct.

Cats that were irradiated effectively with 2 beams directed crosswise, as shown in Figure 7B and C, satisfied the criteria for decerebration as regards rigidity, loss of volitional activity, and lack of temperature regulation. In addition, the aqueduct remained patent as demonstrated by distribution of dye throughout the ventricular system after its injection via an indwelling cannula in the lateral ventricle. However, this cross-fire technic invariably resulted in damage to the trigeminal nerve with consequent facial areflexia; moreover, it seemed desirable to obtain more complete midbrain damage. Parasagittal, parallel orientation of 2 beams, as shown in Figure 7E, obviated the trigeminal damage and spared the aqueduct as well, but this maneuver still allowed some tissue to escape destruction even though the preparation appeared functionally to be decerebrate.

For our purposes, the 4-beam array shown in Figure 9 produced the most satisfactory preparation (Fig. 8). Midbrain destruction was essentially complete, and the cat showed classic signs of sherringtonian decerebration with all cranial reflexes operating briskly below the level of the lesion. The ultrasonic preparation differs from the sherringtonian decerebrate cat in one notable respect—in the latter, after removal of the forebrain, the pupils are widely dilated, whereas, after ultrasonic transection of the midbrain, the pupils are constricted in the characteristic fashion of the low *cerveau isolé* preparation (that is, with forebrain intact but isolated).

Incomplete transection after ineffective irradiation of the midbrain, when it occurred, was readily evident from various indications of residual forebrain influence such as righting,

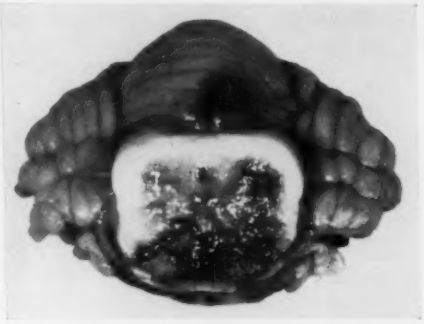


Fig. 8. Gross perfused specimen of midbrain obtained twenty-four hours after ultrasound irradiation with 4-beam sequence at 4 watts per square centimeter for ninety seconds in each position

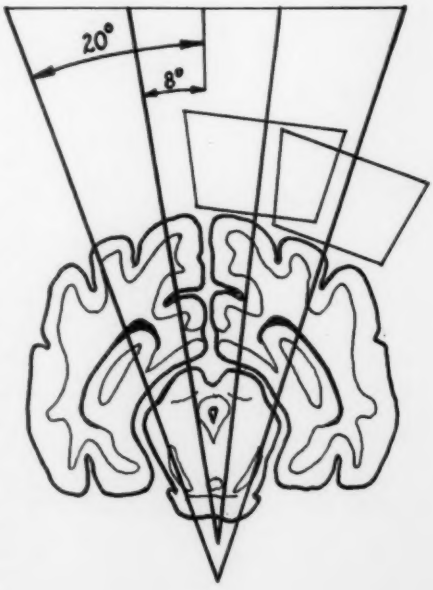


Fig. 9. Scale drawing of the geometric arrangement for ultrasound irradiation used to produce effect shown in Figure 8. Trapezoids correspond to positions of Lucite coupling cone.

LEGEND FOR ILLUSTRATION ON OPPOSITE PAGE

Fig. 10. [a] Effect of 2-beam crossfire irradiation at 4 watts per square centimeter for sixty seconds in each position on vasomotor and respiratory responses to electrical stimulation of the hypothalamus with a fixed electrode over a period of one-hundred-eighty minutes. [b] Control responses to hypothalamic stimulation over a period of one-hundred-eighty minutes after a sham ultrasound irradiation procedure. [c] Uninterrupted record of 4-beam irradiation sequence on responses to hypothalamic stimulation. Note in panels a and c the benign effects of ultrasonic decerebration on blood pressure and respiration.

running movements, and obstinate progression; these are the usual signs of decortication as contrasted with decerebration.

In cats anesthetized with pentobarbital for the ultrasonic procedure, functional effects of midbrain irradiation were not ascertainable until the next day, after recovery from anesthesia. Nevertheless, we have demonstrated in cats anesthetized with ether that full signs of ultrasonic decerebration appear as soon as the effects of the ether have worn off. Regardless of the anesthetic agent employed, all irradiated animals were kept alive for at least twenty-four hours in order to permit development of the lesion. Ultrasonically decerebrated cats have been kept alive for as long as ten days without detectable alteration in their neurologic status.

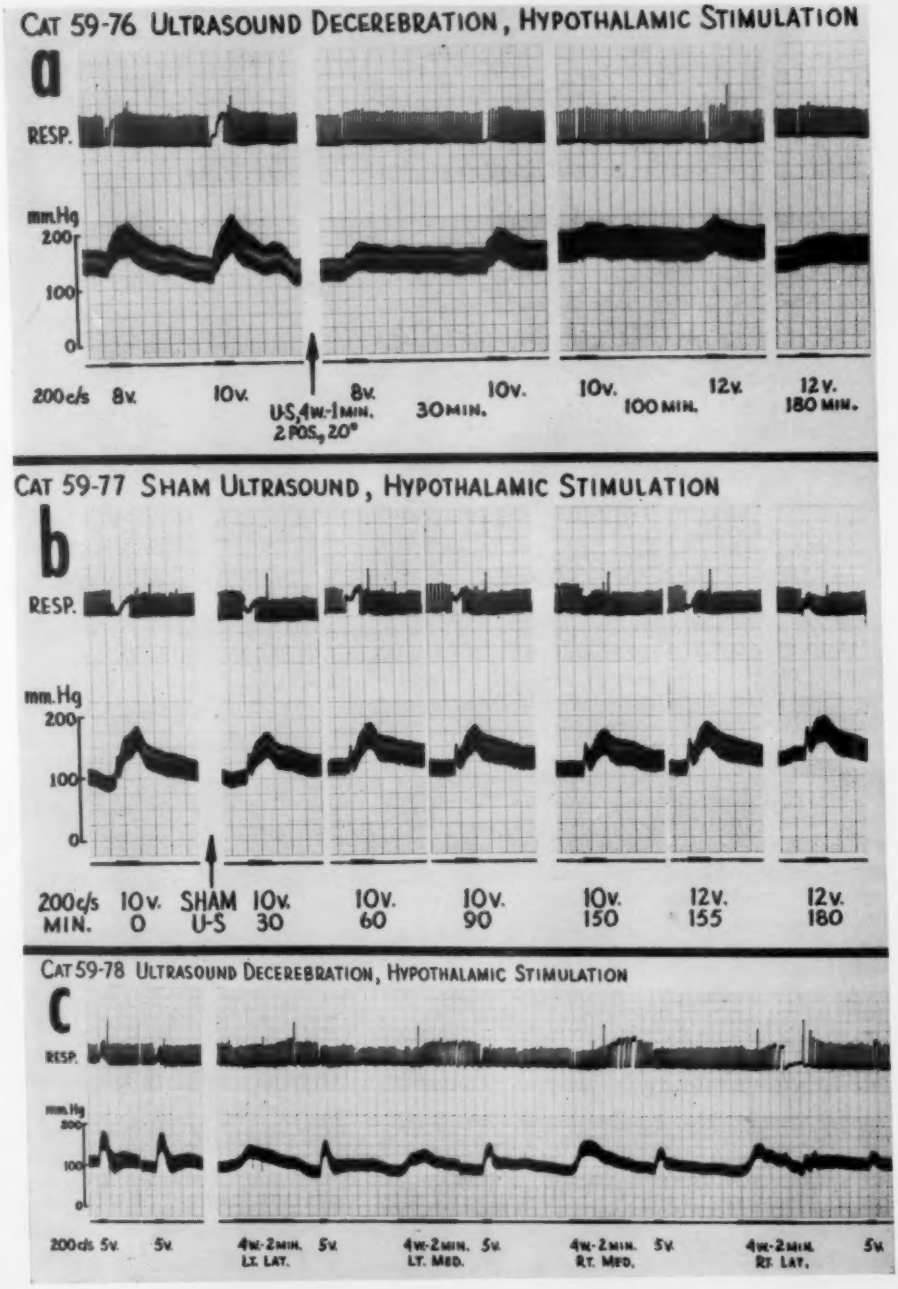
Physiologic evidence of midbrain transection. Vasomotor and respiratory responses to hypothalamic stimulation with a fixed electrode were obtained before and after midbrain ultrasonic irradiation. In Figure 10a is shown the effect of 2-beam cross fire on responses to stimulation of the hypothalamus. At thirty minutes after treatment with ultrasound, the response to 8 volts was essentially eliminated but 10 volts remained partially effective. At one hundred minutes, stimulation with 10 volts was ineffective and 12 volts elicited only a weak response. At one-hundred-eighty minutes, even a stimulus of 12 volts was no longer effective. The experiment shown in Figure 10b served as a control for the experiment just described, that is, after a sham ultrasonic irradiation procedure, consistent responses were elicited over a period of one-hundred-eighty minutes with only slight elevation in stimulus requirement. In another experiment, shown in Figure 10c, effects of a 4-beam procedure were recorded continuously while responses to hypothalamic stimulation were interposed between irradiation steps. Within a period of twelve minutes, the vasomotor and respiratory responses to uniform hypothalamic stimulation were successively diminished, almost to the vanishing point, by progressive ultrasonic transection. The benign influence of ultrasound on the blood pressure is especially to be noted; mean blood pressure during and after the transection procedure did not fall below 90 mm. Hg.

The following facts emerge from a comparison of the 2- and 4-beam procedures. Effective ultrasonic irradiation with 4 beams resulted in prompt interruption of conduction through the midbrain; this agrees with the early presence of the decerebrate state after recovery from ether anesthesia. After 2-beam irradiation, conduction block apparently occurred more slowly in the marginal zone of the midbrain than in the tissue directly in the path of radiation. Thus, 2-beam irradiation causes sufficient damage to effect decerebration, but the process of neurologic impairment is apparently retarded in the fringe area of radiation injury.

DISCUSSION

From the results obtained in our experiments on anemic decerebration, we have reached the following conclusions:

- Arrest of cerebral circulation is not a reliable means of making chronic decerebrate preparations.
- Decerebrate rigidity can be produced by partial cerebral ischemia and, under such circumstances, is reversible in nature. Indeed, the head of a Pollock and Davis "anemic" decerebrate cat receives enough blood to maintain cranial reflexes in the presence of postural rigidity.
- When cerebral ischemia is made sufficiently complete to produce irreversible decerebration, death invariably supervenes as a result of brain edema. Restoration of circulation accelerates the lethal process. Thus, whatever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200c/s 5v. 5v. 4w-2MIN. LT. LAT. 5v. 4w-2MIN. LT. MED. 5v. 4w-2MIN. RT. MED. 5v. 4w-2MIN. RT. LAT. 5v.

may be the cause of edema in response to cerebral anoxia, development of edema is promoted by the restitution of blood flow. This would suggest that the edema results from a local process that is facilitated by capillary leakage rather than from the release of a humoral factor that would be dissipated by blood flow.

Our technic for ultrasonic irradiation of the midbrain provides a relatively simple and reliable means of making decerebrate cat preparations as a routine procedure in the experimental laboratory. The method is rapid, so that it can be performed in less than one hour, requires a minimum of surgical manipulation, merely that of exposing sufficient area of dura for applying the ultrasound, and engenders minimum blood loss, so that the cardiovascular status of the animal is not jeopardized. Finally, the cost of equipment is nominal.

Effectiveness of ultrasonic transection of the midbrain was decided by two functional criteria. The first consisted in judging the neurologic condition of the preparation which, if decerebrate, was characterized by [1] the absence of volitional activity, [2] extensor rigidity, [3] the elicitability of tonic and labyrinthine postural reflexes, and [4] the lack of temperature regulation. The second criterion was perhaps a more rigorous measure of midbrain transection. This consisted in direct evaluation of the functional integrity of descending pathways from the hypothalamus concerned in vasomotor and respiratory control, both before and after exposure to ultrasound. It is known that vaso-and thermoregulatory pathways are distributed diffusely throughout the central gray and tegmentum of the midbrain.[12–14] The distribution of respiratory pathways in the midbrain has not been well defined.

It is to be emphasized that the immediate functional impairment that results from exposure to ultrasound has no readily demonstrable morphologic counterpart. The breakdown of neural structure takes considerably more time to develop; this has already been established by Fry, Brennan, and Barnard.[15] The ultrasonic method we have described is not intended for making discrete lesions and serves a purpose different from that of the focused-beam technic designed by Fry and his associates. Nonetheless, even with unfocused ultrasound, as we have used it, the transmission characteristics are evidently such that the sound energy is concentrated at a given distance from the crystal surface (determined by intensity of radiation), therefore making it possible to transect the midbrain without damaging intervening cerebral tissue. Moreover, we did not have to deal with the problem of relative susceptibility of white and gray matter. The midbrain contains both types of tissue as well as a mixture of the two in the reticular formation. In our experience, adequate radiation dosage caused destruction of both white and gray matter. By contrast, radiation exposure that was inadequate to cause irreversible neurologic deficit also failed to cause detectable brain damage in either white or gray matter. This finding agrees with the conclusion reached by Hueter, Ballantine, and Cotter:[16] ". . . it appears that lesions based entirely on tissue selectivity cannot be produced with reasonable degree of control and safety."

The ultrasonic decerebrate cat is a basic neurophysiologic preparation for which there are many experimental applications. It is useful not only for purposes of studying muscle tone and segmental reflex functions but also for investigating in the isolated forebrain *(cerveau isolé)* fundamental processes concerned in consciousness. Our own studies are aimed at elucidating the actions of drugs injected into the lateral cerebral ventricle. For this purpose, it is essential that the aqueduct of Sylvius be spared by the midbrain transection in order to allow passage of drug solutions into the fourth ventricle. Results of these studies will be published separately.[17]

SUMMARY

"Anemic decerebration" and ultrasonic midbrain transection were evaluated as possible means of preparing chronic, functionally decerebrate cats for research in neuropharmacology.

Regardless of the method employed for producing cerebral anemia, premature death due to brain edema invariably resulted as a consequence of irreversible cerebral damage. In addition, it was found that extensor rigidity is not a reliable index of the decerebrate state

because neurologic recovery followed the development of rigidity in response to partial cerebral ischemia.

With the use of a standard laboratory stereotaxic instrument, a method has been developed for rapid, routine, "bloodless" decerebration of the cat by transection of the midbrain with nonfocused ultrasound. The technic can be employed for both acute and chronic purposes. Physiologic evidence of transection was obtained by electrical stimulation of the hypothalamus and recording of vasomotor and respiratory responses before and after ultrasonic irradiation of the midbrain. Patency of the aqueduct of Sylvius after transection was established by injecting dye into the lateral cerebral ventricle through an indwelling cannula.

The authors wish to thank Dr. P. A. Lindstrom for demonstrating to them his technic of irradiating the brain with ultrasound and Dr. L. S. Goodman for his interest in this investigation and his criticism of the manuscript.

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CASE REPORT

Sarcoid granuloma of the cerebellum

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Capt. W. George Bingham, M.C., U.S.A., and
Capt. Frederick S. Armstrong, M.C., U.S.A.

CURRENT OPINION indicates that sarcoidosis is probably not a specific disease entity but a syndrome—a nonspecific granulomatous reaction to multiple factors that are unknown at present.[1] Reported cases of sarcoid granulomatous involvement of the nervous system are infrequent.[2] Colover[3] found 118 cases in the literature as of 1948; however, the majority exhibited involvement primarily of the peripheral nervous system. Only 1 of 2% of the patients with sarcoidosis manifest nervous system involvement.[4] Only 25 cases with central nervous system and meningeal involvement have been substantiated by necropsy or surgical biopsy;[2] 6 cases with circumscribed, granulomatous, tumor-like masses have been reported.[5] The following case represents a combination of meningeal and intracerebellar involvement, proved by necropsy, in a generalized sarcoid granulomatous reaction.

CASE REPORT

This 23-year-old Negro man first sought medical attention in April 1956 because of mild respiratory symptoms that subsided spontaneously in a few days. Chest roentgenograms were interpreted as showing bilateral hilar and right paratracheal adenopathy. On the basis of the chest film in a patient who was asymptomatic, a clinical diagnosis of sarcoidosis was made. The purified protein derivative intradermal test (PPD), several sputum examinations, and blood counts were negative, and the serum globulin was 4.4 gm. per 100 cc. A positive blood serologic test for syphilis (STS) was interpreted at this time as a false reaction.

The patient remained essentially asymptomatic until October 1957, when vomiting, dizziness, lethargy, and weakness developed. No positive physical findings were noted. Spinal fluid contained 58 cells with 95% lymphocytes and 121 mg. of protein per 100 cc., with a first zone gold curve and a positive STS.

A tentative diagnosis of neurosyphilis was made, and a three-week course of penicillin was given. For three months, the patient improved symptomatically but mild weakness, dizziness, and nausea persisted. The spinal fluid cell count, protein, and serology remained abnormal (see table). In early February 1958, his symptoms worsened and hyperactive patellar reflexes, a tendency to fall to the left, and slight difficulty in coordinating the left extremities developed. The spinal fluid serologic test for syphilis (SFSTS) was reported as being negative at this time. The patient again improved for four weeks, but a relapse again occurred, with severe weakness, generalized hyporeflexia, and urinary retention.

On March 25, he was transferred to Walter Reed Army Hospital. At this time, he was bedridden because of generalized muscle weakness. His deep tendon reflexes were absent, and he had moderate horizontal nystagmus. Spinal fluid at this time was xanthochromic and contained 600 mg. of protein per 100 cc., 26 lymphocytes per cubic millimeter, 33 mg. of sugar per cubic millimeter, and 112 mEq. of chloride. Cultures for predominant organisms and acid-fast bacilli were negative, as they had been in all previous examinations. SFSTS was again positive. Because of this

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RESULTS OF SPINAL FLUID EXAMINATIONS

	Nov. 16, 1957	Nov. 26	Jan. 9, 1958	Feb. 13	Mar. 14	Mar. 25	April 2	May 20	Nov. 7	Nov. 22
Opening pressure (mm. Hg)	140	140	240	110	330	280		190	280	
Globulin	Negative		Negative		Negative	Marked increase		Moderate increase		Negative
Appearance	Clear	Clear	Clear	Clear	Clear	Xantho-chromic		Clear	Clear	
Cells per cu. mm.	58	75	42	54	0	26	6	15	30	
Per cent lymphocytes per cu. mm.	94	75	90	92	0	100	95	100	60	
Per cent polymorphs per cu. mm.	6	25	10	8	0	0	5	0	40	
Sugar (mg. %)		26			40	33		54	33	72
Chlorides (mEq.)		110			144	112		97	120	126
Protein (mg. %)	121	90	108	150	175	600	252	123		14
Colloidal gold	4444443321		3444331000	4444332100	1122333210	3455543211		1122332210		1112210000
Serology	CCF-reaction*		Reactive 0.1 to 1	No reaction	CCF-reaction	Reactive 0.5 & 0.25 not in 0.1		Weakly reactive in 0.5		Nonreactive
T. pallidum immobilization test						Reactive		Nonreactive		

*Cardiolipin Complement Fixation

rapid increase in spinal fluid protein, a cervical block was suspected, but myelograms made with Pantopaque failed to support this. Chest roentgenograms again demonstrated bilateral perihilar and right paratracheal adenopathy. The clinical impression at this time was meningeal sarcoidosis. Prednisone was administered, and there were signs of improvement within a week. At this time, a repeat 1:1,000 PPD was interpreted as weakly positive. Since tuberculous meningitis could not be entirely ruled out, isoniazid and para-aminosalicylic acid were also administered. Soon after this, the SFSTS and spinal fluid Treponema pallidum immobilization test (SFTPI) were reported as positive, and another three-week course of penicillin was given. After approximately four weeks of steroid therapy, the patient was able to walk unaided, his deep tendon reflexes became active, and the urinary retention subsided. The spinal fluid protein and cells lessened considerably, the sugar became normal, and the SFTPI reverted to negative.

Steroid and antituberculosis therapy was discontinued after three months. The patient continued to improve and was discharged from the hospital on July 23, four months after his admission. The only finding at the time of discharge was minimal ataxia on heel-to-toe walking.

He remained essentially asymptomatic until late September 1958, when nausea, vomiting, weakness, and dizziness recurred. He was re-hospitalized on November 4 at his station hospital, where generalized weakness, nausea and emesis, hypoactive deep tendon reflexes, and hepatosplenomegaly were found. His condition worsened, and he was transferred to Walter Reed Army Hospital on November 21. Fluctuating level of consciousness, disorientation for time and place, nystagmus, papilledema, and left cerebellar and Babinski signs promptly developed, and an episode of apnea was noted.

On the day of transfer, a ventriculo-

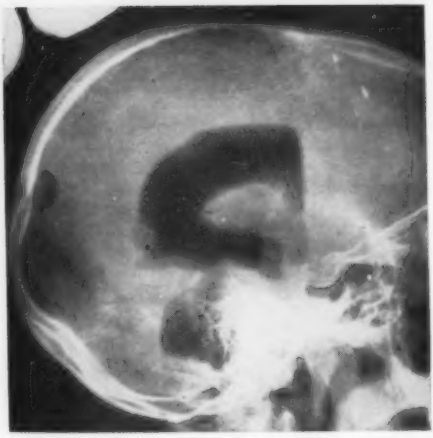

Fig. 1. Ventriculogram showing a dilated ventricular system with a mass lesion protruding into the posteroinferior fourth ventricle

Fig. 2. Photomicrograph of cerebellar cortex showing granulomatous (sarcoid) infiltration of leptomeninges with involvement of adjacent cortex

gram revealed symmetric dilation of the ventricular system and an obstructing mass lesion occupying the posterior half of the fourth ventricle (Fig. 1). A suboccipital craniectomy was immediately performed. The cerebellar tonsils were herniated through the foramen magnum to the level of the second cervical vertebra. The cerebellar hemispheres were separated by a firm, meaty tumor mass involving the inferior vermis. The arachnoid was adherent to this region of the vermis and also to the overlying dura by thickened fibrous bands. The dorsal surface of the medulla was hyperemic and had a roughened, granular appearance. The vermis and hemispheres were readily separated from the medulla, and the obex was visualized. Amputation of the inferior half of the vermis containing the tumor was then performed. As the dissection progressed, it became apparent that the tumor had invaded both hemispheres, particularly the left, where it occupied most of the inferior hemisphere to the level of the restiform body. No areas of cyst formation or softening were noted, and nowhere could a discrete demarcation between tumor and cerebellar parenchyma be found. The patient failed to respond postoperatively and died thirty hours later.

Microscopic examination of the surgical specimens revealed sarcoid granulomas of the cerebellum, with focal calcification, thickening, and fibrosis of the dura.

The general autopsy examination revealed a widespread, noncaseating, granulomatous epithelioid process involving the lungs, mediastinal lymph nodes, liver, spleen, and kidneys. Microscopic examination showed these areas to consist of clusters of epithelioid cells with scanty fibrosis and lymphocytic infiltration. Numerous multinucleated giant cells were present.

The brain weighed 1,365 gm. An insignificant amount of hemorrhage was found in the operative area. Swollen, flattened gyri belied the presence of a moderate amount of cerebral edema. Microscopic study showed similar granulomatous involvement of the cerebellum, particularly over the surface where it extended between the folia (Fig. 2), as well as directly into the parenchyma. Epithelioid cells were also found within the brain stem. The process had not extended over the anterior cerebellum

or into the lateral recesses, nor was there evidence of spread above the tentorium. The process was therefore well confined to a mass lesion involving, primarily, the inferior vermis with local extension into the cerebellar hemisphere and, to a lesser degree, the immediate brain stem. Simultaneous spread along the leptomeninges (Fig. 3) further contributed to early occlusion of the fourth ventricle and onset of characteristic symptoms.

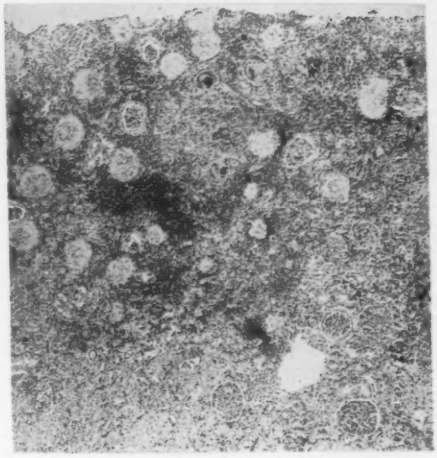

Fig. 3. Photomicrograph showing the dense granulomatous noncaseating tuberculoid nature of the sarcoid process

COMMENT

Sarcoidosis of the nervous system is most commonly manifested by peripheral and cranial nerve lesions.[6] Meningeal lesions have been reported by several authors.[1,2,4,6,7] Infiltrative lesions involving the optic tract and chiasm, temporal lobe, occipital lobe, dura, retina, and tentorium have been reported.[3,6,7] Clinical manifestations and course are quite variable, and the diagnosis is seldom made clinically.[7] In general, the central nervous system lesions are less evanescent than are sarcoid lesions elsewhere in the body.[1]

This case presents many interesting aspects. The spinal fluid findings are unusual and provocative. SFSTS and SFTPI were inconstant, which reinforces the theory of nonspecificity of positive STS reactions in sarcoidosis.[8,9] Each reversion to negative, however, followed a course of penicillin. Earlier studies[10,11] suggested a link between syphilis and sarcoidosis but have not been confirmed.[4,9] The finding of spirochetes in subcutaneous or cutaneous sarcoid lesions[10,11] has not been repeatable. The percentage of positive STS reactions in sarcoidosis in this country has so far been consistent with the prevalent rates for young Negro males.[9] Also, penicillin therapy certainly had no effect upon the course in this case other than for conversion of the serologic studies. Syphilis can produce sarcoid-like lesions;[1] however, there was no indication of syphilitic lesions at necropsy. We therefore must conclude that we are dealing with false serologic reactions.

The abnormally low spinal fluid sugars and chlorides have also been reported in Pennell's[6] series. The remarkably elevated spinal fluid protein with xanthochromia has been reported in another case as quoted by Colover.[3]

An infectious etiology was suggested by the lowered spinal fluid sugar and pleocytosis, but all cultures were negative.

Tuberculosis was suggested by the early clinical picture, which resembled tuberculous meningitis, and by the weakly positive PPD. The chest roentgenograms and autopsy findings, however, were consistent with the diagnosis of sarcoidosis, and necropsy findings did not disclose any tuberculous lesions or acid-fast bacilli. The conversion of the PPD was probably a side effect of steroid therapy—a unique interaction of the tuberculin skin reaction, sarcoidosis, and cortisone, reported by Pyke and Scadding.[12]

Of special interest is the remarkable recovery coincident with steroid therapy. Earlier reports of the effectiveness of steroids in central nervous system sarcoid were disappointing.[6,13,14] However, 2 successfully treated cases have recently been reported.[5,15] In a disease such as sarcoidosis, which is characterized by spontaneous remissions, a more comprehensive study is required before any form of therapy can be evaluated with validity.

SUMMARY

A pathologically proved case of sarcoid granulomatous involvement of the cerebellum and meninges has been presented. Other unusual

aspects included intermittently positive serologic reactions, a highly elevated spinal fluid protein level, and very low spinal fluid glucose and chloride levels. A remarkable recovery was coincident with steroid therapy. This case represents the seventh instance of a circumscribed, tumor-like, intracranial mass reported in the literature.

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Neurology

BOOK REVIEWS

Neurology

by Roy R. Grinker, M.D., Paul C. Bucy, M.D., and Adolph L. Sahs, M.D., 5th ed., 1,386 pp. Charles C Thomas Co., Springfield, Ill., 1959. $24.50

In this fifth edition, *Neurology* has acquired a third author, Adolph Sahs, and, as a result of the industry of Bucy and Sahs, this text, which has always stood out in front, has been completely revised and greatly expanded. It has been rewritten and reset throughout in new type.

Upon its introduction in 1934 by its pioneer author, Roy R. Grinker, *Neurology* was the only textbook dedicated to the presentation of disorders of the nervous system upon a framework of morphologic structure and neurophysiologic function. It was designed to explain symptoms in terms of the functioning of the nervous system, the only logical way for the student to understand the nature of symptom complexes that are so baffling without the knowledge of functional anatomy.

Since the fourth edition in January 1949, great advances have been made in neurophysiologic investigation and anew science, neurochemistry, has entered the neurologic field. The need for a complete revision was recognized. To this end, the authors have added much new material in neurophysiology, neurochemistry, and hormonal and endocrine physiology, requiring rewriting of many chapters and the addition of a new chapter on neurochemistry (Neurochemistry and Metabolic Diseases). The expanded knowledge of the structure and function of the hypothalamic-hypophysial region, the reticular formation, the limbic system, and the cerebellum has required much revision of the old text.

Advances in the treatment of infections of the nervous system in the past ten years and new surgical technics have been incorporated in appropriate chapters on infections, dyskinesias and dystonias, vascular malformations, and brain tumors. The close relationship of systemic disease and the nervous system has been duly recognized by the addition of a new chapter; The Neurological Manifestations of Certain Medical Diseases.

With the inclusion of much new material, the fifth edition has become a large volume of 1,386 pages, weighing 7 lb. In spite of its bulk, the book remains open without assistance from the reader. It is richly illustrated by tables, diagrams, and photographic material of unusual clarity. Instead of the usual bibliography at the end of each chapter, an extensive bibliography, arranged alphabetically by authors, appears at the end of the text (132 pages of documentary references for the avid student).

This is a superb achievement by 3 men each eminent in his field of neurologic science, all investigators and teachers, together combining neuropathology, neurophysiology, the practice of psychiatry, neurosurgery, and clinical neurology. It is a text that every medical student should own, an indispensable reference for physicians and especially students and practi-

tioners in the field of neurology (neurosurgeons, clinical neurologists, and psychiatrists).

The authors have drawn widely upon others for special assistance in the preparation of certain phases of the text material and have given credit to these men by name in the preface. The authors voice their regret that the size of the volume does not permit the addition of the neurologic aspects of behavior. The reviewer foresees the need for making available in textbook form the developments in this area of neurophysiology. Much is now known of the relation of anatomic structure and function to learning, memory, and behavior, with significant implications in psychiatric and psychosomatic disorders. Perhaps, in the future, a two-volume text will be feasible.

M.G.M.

Postvaccinial Perivenous Encephalitis

by Ernst DeVries, 181 pp., ill., Elsevier Publishing Co., Amsterdam, 1960. $7.75

Although this monograph contains a great deal of information of clinical, epidemiologic, and pathologic interest concerning postvaccinial encephalitis and allied conditions, the book is not written as a systematic or didactic exposition of the topic. Rather, it is designed to bring forth evidence to support the author's own individual point of view about the nosologic significance of the various myeloencephalitic reactions that at times follow vaccination. It is his conviction that the lesion which he calls "microglia encephalitis" is a specific tissue reaction for uncomplicated postvaccinial encephalitis. The essential, and virtually the only, features of the lesion are foci of perivenous demyelinization within which there occurs proliferation of microglia, marginal gliosis, and, occasionally, patchy, more diffuse infiltration by glia, with or without small perivenous cuffs of lymphocytes.

This restricted type of encephalitic reaction is to be sharply separated from other types of disseminated encephalomyelitis, sometimes also perivenous, which often are seen to follow vaccination and several exanthems. In particular, it is to be differentiated from the less specific toxi-infectious encephalopathic reactions that may develop with a great variety of acute infections including vaccinia and the exanthemas and are characterized by severe changes of the vessel walls, perivascular hemorrhage, and hematogenous exudation. When the two types of lesion are encountered in the same brain, the presumption is that the vaccinia was associated with another acute infection such as pneumonitis.

The author points out that, while there are sometimes clinical differences between the types of postvaccinial encephalitis, such are by no means as certain as the pathologic ones. He points out also that microglia encephalitis is never seen in children under 2 years of age or after revaccination when there is an immunity reaction of the skin.

The author's conclusions are based upon a careful pathologic study of 62 Dutch cases of postvaccinial encephalitis, some experimental material, and a thorough-going study of the literature dealing with this group of diseases. The thesis that the author presents is a controversial one, and his dictum, "We accept that in biology as well as in physics the same cause, acting on the same tissue must have the same effect" will surely meet with disagreement, at least in the way in which he applies it. The book will, however, be of considerable interest to all who are interested in the demyelinating diseases and the phenomena of local tissue sensitivity in the nervous system.

R.B.R.

Clinical Applications of Diagnostic and Therapeutic Nerve Blocks

by John J. Bonica, 354 pp., Charles C Thomas, Springfield, Ill., 1959. $8.75

In this concise monograph, the author describes the principles and technics of nerve blocks. His intended audience is any practitioner interested in the subject. For this reason, introductory material is included which might seem superfluous to a specialist in anesthesiology or neurology but is quite essential to a novice in the field.

The subject is covered in all its aspects: anesthetic and blocking agents and the details of the technics for the injection of sympathetic and peripheral nerves, nerve roots, and subdural and subarachnoid spaces. The complica-

tions are enumerated. Brief mention is made of the various conditions that may be treated by nerve block.

The text is well illustrated with halftone and line drawings. A selected list of references from the world literature is given, and a detailed 50-page index is appended.

Perhaps the most difficult aspect of diagnostic nerve blocks for most practitioners and specialists is the interpretation of the result. Is the subjective appraisal by the patient sufficient for valid judgment? Or must one carefully control the test by using multiple injections, some with saline and some with a local anesthetic agent? Is one justified in "fooling the patient" in order to arrive at a conclusion? And how can the physician be sure the patient is not consciously or unconsciously fooling him? These questions are not discussed in great detail in this monograph, but they are difficulties that deter many physicians from using diagnostic blocks extensively.

This monograph should be a useful addition to the book shelf of every neurologist who uses nerve blocks as a part of his therapeutics. For the neurosurgeon and anesthesiologist, it will be of daily assistance and may well encourage them to extend their therapeutic endeavors into new fields.

A.E.W.

Actualités Neurophysiologiques

published under the direction of A. M. Monnier, 276 pp., ill., Masson & Cie, Paris, 1959. $6

Translated literally, this French paperback is a "news of the day" of neurophysiology. It is the first of a series designed to report conferences held at the Faculté des Sciences de Paris. The papers, written in French, are the work of a long list of illustrious neurophysiologists, including Lord Adrian, Guillot, Hartline, Arvanitaki-Chalazonitis, Stämpfli, Monnier, Granit, Paillard, Margaria, Wyss, Bonvallet, Katz, LaPorte and Bessou, Humbert, Colle and Massion, Coraboeuf, May, and Malmejac. The contributions cover sensory physiology, physiology of nerve fibers, physiology of reflexes, central neurophysiology, neuromuscular physiology, cardiac microelectrophysiology, developmental physiology of nerves, and neurohumoral phenomena, each author choosing a subject upon which he is an authority.

The selection of topics is excellent and the format good; the papers are, for the most part, brief and not exceptionally technical. The book is certainly to be recommended to specialists in neurophysiology. It and its successors will also have the interest of medical libraries and of those building personal libraries representative of current thinking in the neurologic sciences.

The Neurologic Examination of the Dog—With Clinicopathologic Observations

by John T. McGrath, D.V.M., 2d ed., 281 pp., Lea & Febiger, Philadelphia, 1960. $7

Although the title of this book suggests that examination technics are emphasized, the subtitle should be stressed, for much information on clinical and pathologic aspects of canine neurology is included.

The initial sections of the book review technics in eliciting the history and performing the physical examination. A general review of neuroanatomy follows. The clinical neurologist will find much of this quite elementary except for the specific information relating to the dog brain. The cerebrospinal fluid examination of the dog is also considered.

The remainder, and largest portion, of the book considers clinical and pathologic aspects of various neurologic diseases of the dog. Congenital, toxic, metabolic, traumatic, infectious, neoplastic, and vascular lesions of the brain, vertebral column, spinal cord, and meninges are included.

The book is well written. The photographs are plentiful and of good quality. The neuropathology appears very accurate. The author has acknowledged assistance from Dr. Helena Riggs in the preface.

Although this book will be of most value to the veterinarian who desires to increase his knowledge of canine neurologic disorders, it is also to be recommended to research workers using the dog. Whether it will appeal to the clinical neurologist will depend very much on individual interests. Frankly, this reviewer

found it quite fascinating to read, for example, that brain tumors usually occur in boxers and Boston terriers and that idiopathic epilepsy is most prevalent in cocker spaniels, French poodles, and wire-haired fox terriers and to learn about the incidence and clinical picture of other neurologic diseases in various breeds.

Considering the widespread use of the dog for research and the myriads of observations reported after experimental lesions, one cannot help but think that the study of spontaneously occurring diseases in the dog and other animals is somewhat neglected. Such study might well advance our knowledge of human neurologic problems. This book will undoubtedly stimulate interest in canine neurology.

K.R.M.

Chemical and Molecular Basis of Nerve Activity

by David Nachmansohn, 235 pp., Academic Press, Inc., New York City, 1959. $7.50

For more than twenty-five years, Dr. David Nachmansohn has been identified with studies on the metabolism of acetylcholine and the functional role of this compound in conducting tissues. He has approached these problems from the standpoint of biochemist and enzymologist rather than that of physiologist or pharmacologist, as has usually been the case with those working in this area. He was an early convert to the theory of humoral neuromuscular and transynaptic transmission of impulses but became, quite properly, critical of the principle of inferring physiologic roles from the pharmacologic actions of even naturally occurring substances. Moreover, his extensive studies on the enzyme systems responsible for the intracellular synthesis and hydrolysis of acetylcholine, together with accumulating neurophysiologic evidence pointing towards a unitary basis for conduction and synaptic transmission, led Nachmansohn, with J. F. Fulton, to propose that the role of acetylcholine was actually an intracellular or, at least, intramembranous one, that its function was to alter membrane permeability to ions, and that the process was essentially the same along the length of the axon as at its terminal. In this hypothesis, therefore, no essential difference is envisaged between conduction and synaptic transmission. The current flow in the presynaptic axon terminal is regarded as the adequate stimulus for altering the potential of the postsynaptic membrane.

This theory has not, in general, been accepted by neurophysiologists and neuropharmacologists and, indeed, has been widely and often violently attacked since it was first proposed in 1940. Nevertheless, Nachmansohn has stood his ground, in a number of instances has been successful in disproving evidence offered against his theory, and, in some cases (notably that of di-isopropyl-fluorophosphate), has even turned such evidence to his own advantage. Certainly, during this twenty-year period, much excellent work on the enzymology and physical chemistry of conducting tissues has come from his laboratory. Nevertheless, in spite of the many plausible and unifying features of Nachmansohn's theory, it has generally been regarded as unproven and largely supported by circumstantial evidence only.

The progress of Nachmansohn's thinking on these matters, the record of controversy, and the actual investigations of the author and his associates are thoroughly documented in this volume. It starts with chapters dealing with the general physiology of nerve activity, then goes on to a review of the author's studies on acetylcholinesterase and his conclusions as to its essentiality for axon conduction, and thence to the physical chemistry of acetylcholine hydrolysis by this enzyme. The exemplary studies of I. B. Wilson, carried out in the author's laboratory, on the nature of acetylcholinesterase inhibition by nerve gases and insecticides and how this may be reversed by compounds with a requisite chemical configuration are well described. Also included are chapters on the choline acetylase system and current studies on the acetylcholine receptor protein. The volume concludes with discussions on the nature of membrane permeability changes and the possible role of acetylcholine and cholinesterase in bringing about these changes during both axonal conduction and synaptic passage of impulses.

While the author's position is forcefully stated and defended in this book, the latter also does have the attributes that often have

been criticized in Nachmansohn's previous writings. There is the factual error of including the optic nerve in the peripheral sensory nervous system, which is not unimportant, since it is used as an argument for the generality of the acetycholine system in peripheral sensory as well as motor fibers. There is a tendency to accept as conclusive proof for the author's doctrine observations that are merely consistent with it. Contrariwise, there are peremptory dismissals of data and opinons of others which are contrary to those of the author with just a comment concerning the inadequacies of methods or reasoning used but no adequate explanations for such statements. Nor is it hard to discern from these pages the personal conflicts that have made sober appraisal and discussion of these problems so difficult.

This book can be highly recommended as a thorough and able presentation of the author's work on the acetylcholine system and a succinct hand persuasive argument for his theory concerning this compound's role in the physiology of conduction. It must be the reader's task to decide for himself how effectively the author has presented his case.

A.P.

Handbook of Physiology:
Section I, Neurophysiology

editor-in-chief, John Field, section editor, H. W. Magoun, Vol. II, pp. 781-1439, American Physiological Society, Washington, distributed by Williams & Wilkins Company, Baltimore, 1960. $20

The second volume of the Section on Neurophysiology of the *Handbook of Physiology*, like the first volume, is an outstanding reference work. It opens with a discussion of motor mechanisms and the general principles of motor integration by Derek Denny-Brown, followed by discussions on sensorimotor cortical activities, the pyramidal tract, the extrapyramidal motor system, spinal mechanisms in somatic activities, autonomic functions, and central control of eye movements, respiration, feeding, drinking, bladder function, and so forth, by equally authoritative authors.

The introduction to the section on central regulatory mechanisms is written by Dr. F. Bremer and is followed by discussions on the cerebellum, reticular formation, thalamocortical relations, intrinsic systems of the forebrain, the cingulate and associated areas, the hippocampus, and the amygdala.

This volume is a continuation of the first. The various discussions are thorough and complete, and the authors are known for their familiarity with the various subjects discussed as well as for their ability to present their material in a logical and readable fashion. This undoubtedly is the most exhaustive reference work today on neurophysiology. Although the volumes are addressed primarily to professional physiologists, they should also have great interest and value for clinicians and nonphysiologists working in allied neurologic fields.

R.N.D.

Biochemistry of Human Genetics

edited by G. E. W. Wolstenholme and C. M. O'Connor, Ciba Foundation Symposium, 347 pp., ill., Little, Brown and Co., Boston, 1959. $9.50

This volume contains the papers and discussions of a small symposium (29 participants) on human genetics from a primarily biochemical standpoint held at the Naples Zoological Station in May 1959 under joint auspices of the Ciba Foundation and the International Union of Biological Sciences. The small number of participants should in no way be construed as a limiting factor in the comprehensiveness of the coverage. On the contrary, this is an extraordinarily interesting and stimulating volume, although, as is usual with Ciba Symposia, the treatments are at a very high level of sophistication. Those not conversant in some detail with the language and methods of genetics and/or biochemistry may have difficulty with some of the papers and discussions; yet I would urge that such problems not deter the reader from going on to glean much that is not only understandable to all, regardless of background, but is also fascinating and important.

The subject matter is primarily concerned with human blood studies—a limitation that is understandable from both the genetic and biochemical standpoints when one considers

the species under discussion. Nevertheless, the relevance of the specific as well as the general aspects to neurology is self-evident. The principal papers comprised 7 as follows: Genetical Analysis in Man (Penrose); Biochemical Genetics as Illustrated by Galactosemia (Kalckar); [Serum] Cholinesterase Types (Kalow); Genetical Variation and Sense Perception (Kalmus); Genetics of Primaquine Sensitivity of Erythrocytes (Childs and Zinkham); Chemical and Genetical Units of the Hemoglobin Molecule (Itano, Singer, and Robinson); and Genetical Control of Protein Structure: The Abnormal Human Hemoglobins (Hunt and Ingram).

Following these were 7 "short" communications on fetal myoglobin (Rossi-Fanelli and associates), plasma protein variants (Harris and associates), haptoglobins and transferrins (Smithies and Connell), blood groups (3 papers: Morgan, Watkins, and Ceppellini), and the gamma globulins (Grubb). There was also a panel discussion on the use of tissue culture as a tool for solving some of the problems, the panel including Eagle, Lederberg, Luria, Burnet, and Neel among many others. The symposium was closed with a paper on the Mechanism of Gene Action (Brenner) and a general discussion.

It is perhaps unfair to single out specific papers when all were of a high order of excellence, but I particularly recommend the presentations of Kalckar, Kalmus, Itano and associates, Hunt and Ingram, Morgan, and Brenner, plus the remarks by Eagle on tissue culture problems (p. 288 ff.). As indicated above, when read without the appropriate background contexts, this volume may prove difficult for some or may not be fully appreciated. Perhaps the prior reading of the recent books by Anfinsen and Hsia would prove useful for orientation purposes. In reading this symposium volume, one is impressed by 3 general points: the extraordinary advances that have recently been made in human genetics, the extreme relevance of biochemistry and physical chemistry to genetic problems, and the rapidity with which geneticist, biochemist, and clinician are closing ranks upon many of these phases. Finally, I would echo Dr. Neel's remark (p. 323) that it is refreshing to have a whole symposium devoted to this subject during which no one has mentioned radiation effects but concentrated on the substrata that must be understood before radiation can be intelligently fitted in.

The volume can be highly recommended and should stand high on the list of required reading for all in neurology.

D.B.T.

Aids to Neurology

by E. A. Blake Pritchard, M.D., F.R.C.P., 480 pp., Bailliere, Tindall, and Cox, London, distributed by Williams & Wilkins Company, Baltimore, 1959. $4

This is the second edition of a small book that has gone through five printings since the first edition was published in 1932. It is designed to provide an introduction to the basic essentials of neurology for students in the earlier years of their general medical training. In it, the various neurologic syndromes and diseases are described in summarized form suitable for ready reference. The book emphasizes the clinical approach and presents the common clinical pictures. The relationship of anatomy and physiology to the development of clinical symptoms is considered separately in a special chapter that appears after the clinical sections.

This small book, written by an experienced clinical neurologist, can serve as an excellent guide for students and practitioners.

R.N.D.

Practical Neurological Diagnosis

by R. Glen Spurling, 6th ed., 284 pp., Charles C Thomas Co., Springfield, Ill., 1960. $6.75

The fact that this is the sixth edition of Spurling's text speaks for its usefulness and wide acceptance. It also emphasizes the growth and importance of the neurologic sciences.

The usual sequence of history taking and examination is followed, with guides and suggestions for the elicitation of historical data and neurologic findings. Anatomic, physiologic, and clinical correlations accompany the text, supplemented by anatomic reproductions and photographs. The text includes a brief outline of the neurologic examination (after Cushing),

a glossary of terms commonly used in neurology, and references to texts and articles useful to all students of neurology.

Medical students and graduate students of neurology and neurosurgery will find this a useful guide. Practicing physicians will find the simplicity and clarity of this text helpful in examination and clinical evaluation of patients in office and hospital practice.

M.G.M.

The Postnatal Development of the Human Cerebral Cortex

by J. LeRoy Conel, Vol. I, Newborn, 164 pp., ill., 1939; Vol. II, 1 Month, 144 pp., ill., 1941; Vol. III, 3 Months, 158 pp., ill., 1947; Vol. IV, 6 Months, 177 pp., ill., 1951; Vol. V, 15 Months, 220 pp., ill., 1955; Vol. VI, 24 Months, 292 pp., ill., 1959; Harvard University Press, Cambridge, Mass. Vol. VI: $12.50

With the publication of the sixth volume on postnatal development of human cerebral cortex, the monumental work of Conel is extended from the cortex at 15 postnatal months (Vol. V) to the cortex at 24 months. Thus, a solid abutment has been laid down for a future bridge to span the gap in the knowledge of the normative data on morphologic growth and maturation of the cerebral cortex in man from birth to, eventually, the senium. All 6 volumes follow the same plan of presentation of material. To date, a total of 39 cerebra of infants from birth to 2 years (from 5 to 9 specimens for each of the 6 age groups—the newborn, 1 month, 3 months, 6 months, 15 months, and 24 months) were used in this long-term normative research.

Careful encephalometric and photographic records were prepared for each specimen. All specimens were fixed in 10% formalin by perfusion. The left hemispheres were used for cresyl-violet stain on paraffin sections and for Cajal silver impregnation on celloidin sections. The right hemisphere was used for Weigert stain of myelinized fibers and for Golgi-Cox method for impregnation of cell bodies and their dendritic and axonal plexus in the cerebral cortex. Von Economo and Koskinas' definitions and nomenclature of cortical areas were chosen and followed throughout. This was a fortunate choice because of the unsurpassed clarity of Von Economo's cytoarchitectonic schema and of the quantitative documentation this reference work provides on the width of the cortical laminae, the cell density, and the cell size in the adult. A total of 37 cortical areas were selected, following the criteria of their topographic relation to the surface landmarks in each brain and their cytoarchitectonic characteristics. The sample blocks of cortex were selected from identical loci in each brain.

The architectonic analysis of the development of each area was followed from birth to 2 years with reference to 9 parameters of the morphologic change observable with the methods used during the postnatal development of the cerebral cortex: [1] the width of the cortical plate and of the individual lamina in each area; [2] the cell count per 0.1 cu. mm. of gray matter in each lamina; [3] the size of nerve cells in terms of largest axial and transverse or basal diameter; [4] the appearance, degree of differentiation, and shape of Nissl's substance; [5] the appearance and differentiation of neurofibrils; [6] the diameter and number of dendrites and of axonal collaterals; [7] the appearance and characteristics of the "pedunculated bulbs" on the dendrites and cell bodies of the cortical neurons; [8] the diameter and number of the exogenous fibers; and [9] the spread and distribution of myelinized fibers in the cortical plate. The number of cells per unit volume of gray matter in each lamina, the width of laminae in microns, and the measurements of the size of cells are presented for each age in the form of tables in each of the respective volumes.

Each volume is illustrated with an atlas of about 100 plates, which provide a visual documentation of the gross surface morphology of the brain for each age group, the cytoarchitectonic pattern of each area in microphotographs of cresyl-violet and Cajal silver pyridine preparations, and the fibroarchitectonic pattern of the dendritic and axonal plexus in Golgi-Cox preparations. Each of the latter preparations is accompanied by beautiful camera lucida drawings of the total complex of the cortical neurons with their dendritic and axonal plexus as it appears when the technical artifact of unavoidable precipitation of silver granules in Golgi preparations is abstracted

from the image. The plates of the graphic atlas and the tables of measurements made available in the 6 volumes of this enormous work represent a stupendous yet systematically and orderly arranged stockpile of fundamental normative data on growth and development of the cerebral cortex in man from birth to 2 postnatal years. The documentation methodically collected by the author during some twenty-five years of a truly missionary work of a dedicated explorer is so large that it would call, as no doubt it will, for teams of neuromorphologists and statisticians to grasp its full meaning and to construct working hypotheses on these data.

It seems that so far 3 fundamental general propositions have emerged from this work:

1. Flechsig's hypothesis based on his myelogenetic studies of differentiation of the cerebral cortex spreading outward from the primary projection zones to the probably athalamic terminal zones has been confirmed and is supported now with precise evidence encompassing 8 other parameters of measurable morphologic changes which occur in the cerebral cortex during its postnatal development.

2. The differentiation of the cortical plate advances from allocortical formations of the innermost rhinencephalic zones of the hemispheres to the intermediate mesocortical (limbic and insular) zones and from these zones to the homotypical isocortical zones of the convexities of the frontal and temporoparietal and occipital lobes.

3. The granulose primary sensory projection areas behind the plane of Rolando fissure and those in the posterior (granular) limbic and in the retro-Rolandic supralimbic areas of the parietal lobe differentiate, at least in early postnatal months, somewhat in advance of the frontal gigantopyramidal and anterior (agranular) limbic and insular and the pre-Rolandic supralimbic areas of the frontal cortex.

In the first 4 volumes, the author remained with admirable restraint at a descriptive factual level, allowing himself not a single generalization until the fifth volume on the cortex at 15 postnatal months. In the summarizing chapters of the fifth and sixth volumes, he discussed at some length only one conclusion derived from his long and painstaking study. The conclusion challenges the widely held notion of the contiguity of axonal terminals with the dendrites and cell bodies in the cerebral cortex through direct synaptic contacts ("boutons terminaux"). In none of his Golgi-Cox, Cajal, and Bodian preparations did he ever observe such direct synaptic contacts in the cortex. He favors the position that the dynamic interaction between the neurons in the cortical neuropil is effected through the changes of potential in the electromagnetic fields created between the axonal fibers and the somatic and dendritic surfaces of the neurons and that these changes of potential and, therefore, conduction depend on the orientation and reciprocal relation in space of the conducting fibers and on the physicochemical equilibria in the fibers and in their immediate milieu rather than on the direct contact of the axonal fibers with the other neurons and their dendritic branches across a synaptic membrane.

The 6 volumes so far published represent, by all criteria, an outstanding contribution of American scholarship made possible under farsighted and discerning auspices of the Department of Pathology of Children's Medical Center in Boston. For those who had the discrimination to collect these stately volumes as they appeared over the past twenty years, they bear something of a personal compliment and will represent one of the more explicit marks of the acumen of the reference libraries in the institutions of neurobiologic learning and research. Those who have consulted them will wait with impatience and hope to see the publication of the seventh volume on the cortex of the 6-year-old child.

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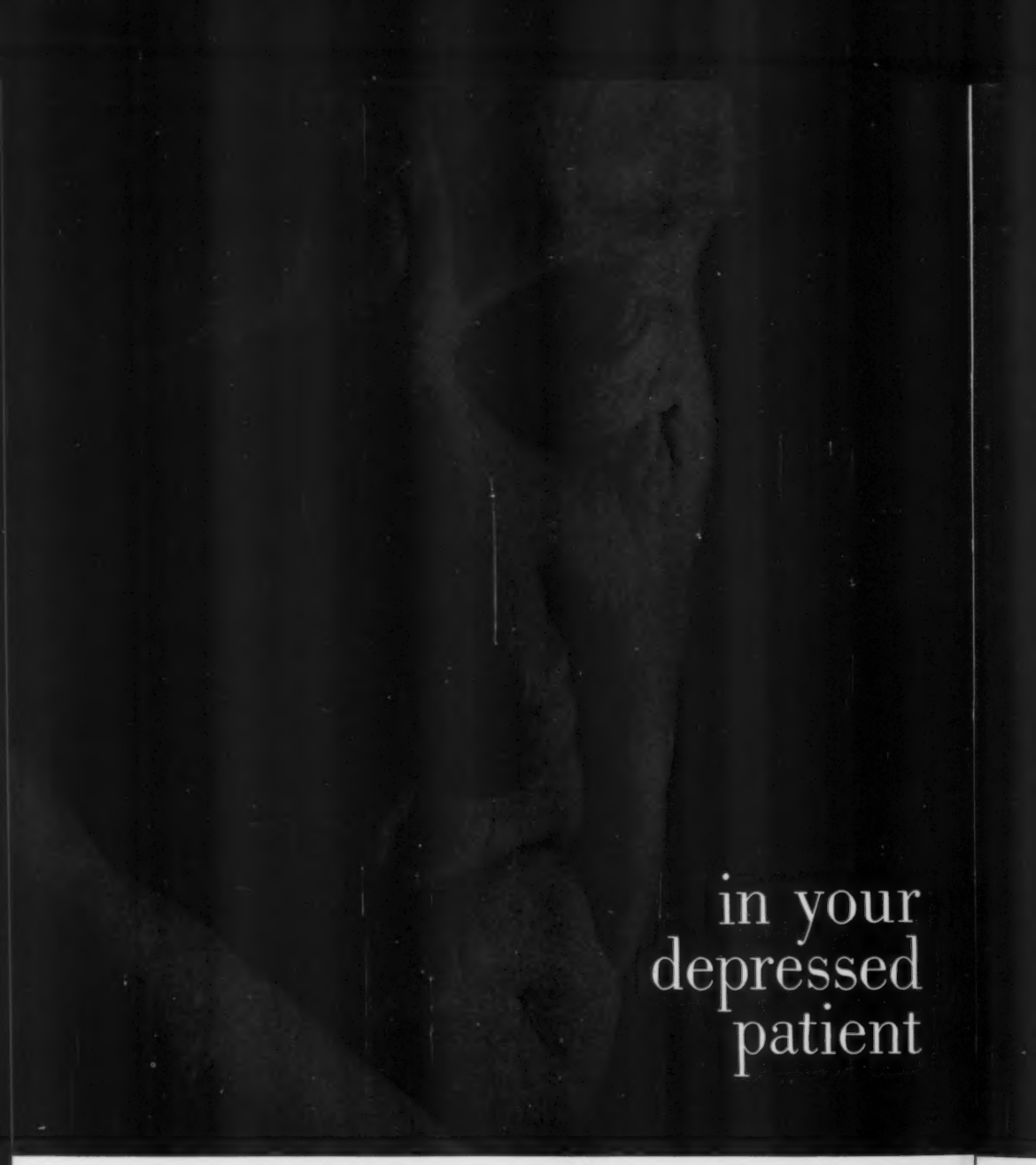

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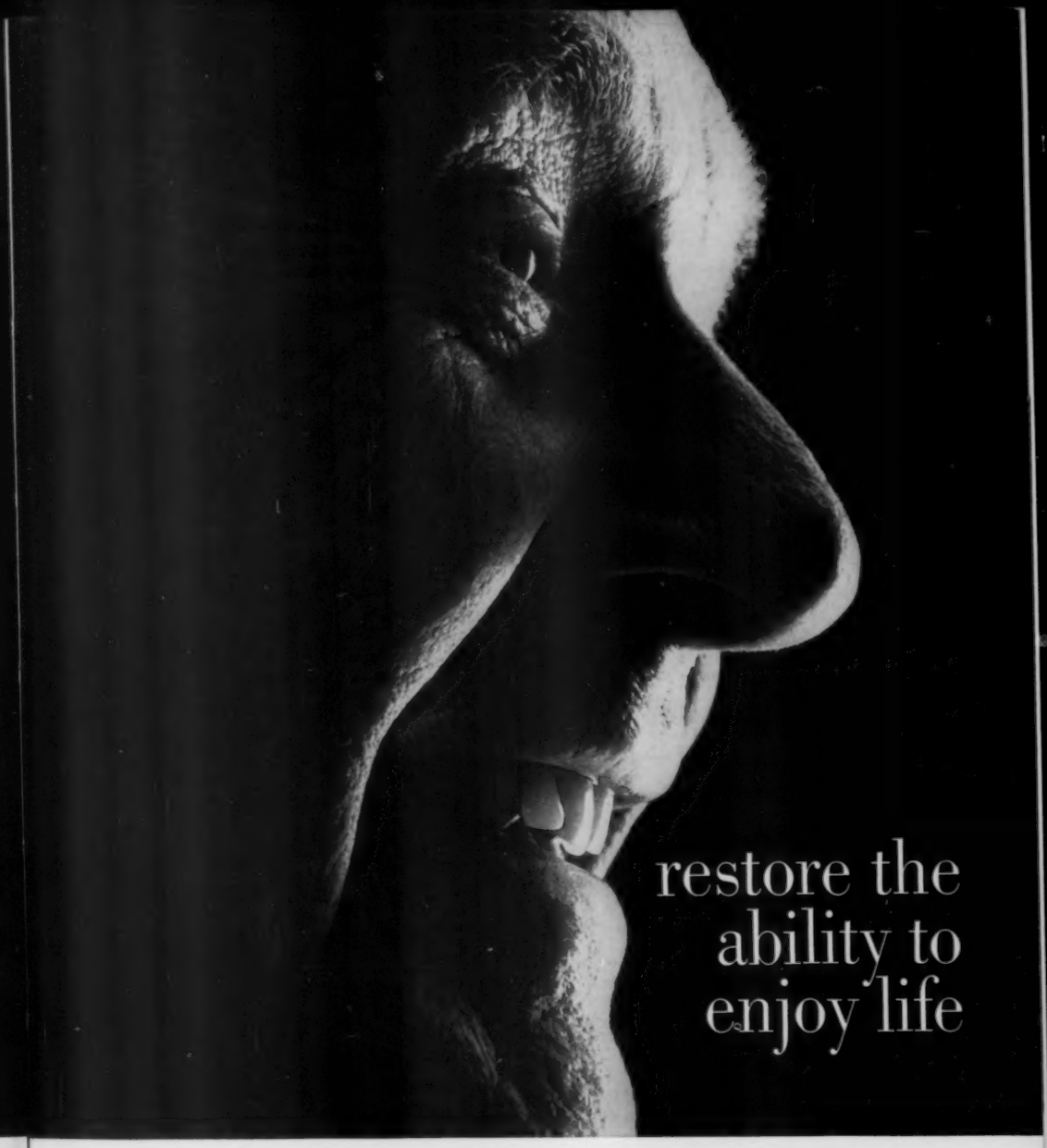

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NEWSLETTER

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Katzman Wins Mitchell Award Robert Katzman of the Albert Einstein College of Medicine in New York was the recipient of the 1960 S. Weir Mitchell Award for his paper "Electrolyte Distribution in Mammalian Central Nervous System Are-Glia High Sodium Cells." Katzman, now an active Academy member, was a junior member when he submitted his prize-winning essay. The S. Weir Mitchell Award Committee is composed of Arnold P. Friedman, Chairman; Sidney Carter; and Russell N. De Jong. The Award is sponsored by the Women's Auxiliary of the Academy for the best essay on fundamental or basic neurologic research submitted by a junior member of the Academy. The contest is open only to AAN junior members who are in training for certification in neurology. ... The deadline for the receipt of manuscripts for the next Award is January 1, 1961. Besides the cash honorarium of $200, the selected essay will be read by the author at the 1961 Annual AAN Meeting in Detroit. The recipient's transportation fare also will be paid by the Academy. The Academy reserves the right to publish the selected manuscript. Manuscripts must be typewritten, double-spaced, and submitted in quadruplicate to Mrs. J. C. McKinley, Executive Secretary, AAN, 4307 East 50th Street, Minneapolis 17, Minnesota.

Moossy Visits Oslo and Copenhagen John Moossy, now conducting a pilot study on methodologies applicable to the geographic pathology of cerebrovascular disease, has begun a series of visits to European centers to confer with outstanding European neurologists, neuropathologists, and pathologists. His first visit was to Oslo, where he consulted with Professors S. Refsum, O. Thorgesen, and Drs. A. C. Løken, K. Arentsen, K. Westlund, W. Harkmark, and E. Dahl... After Oslo, Moossy visited Copenhagen and consulted with Professor Mogens-Fog and Dr. Erna Christensen. Here also he found interesting investigations being conducted on cerebral-arterial disease by Drs. Bent de Fine Olivarius (clinical aspects) and Badsberg (pathologic aspects). In commenting on his trip, Moossy said, "Neurology and neuropathology in Oslo and Copenhagen are vigorous and active disciplines which work closely with related medical disciplines, such as pathology on cerebrovascular disease and other common problems."

Pavlovian Conference on Higher Nervous Activity

A Pavlovian Conference on Higher Nervous Activity is scheduled to be conducted at Town Hall, 123 West 43rd Street, New York (October 13 through 15, 1960). The Conference is sponsored by the Section of Biological and Medical Sciences and the Division of Psychology of the New York Academy of Sciences, and by the Academy of Medical Sciences of the Union of Soviet Socialist Republics (Moscow). The sessions, which are to be co-chaired by Nathan S. Kline of Rockland State Hospital and Gregory Razran, Chairman of the Division of Psychology of the New York Academy of Sciences, will feature 5 important topics relating to higher nervous activity. Each of the major topics will be under session co-chairmen as follows: "Structure and Function," Robert B. Livingston (Bethesda) and Hans-Lukas Teuber (New York); "Cortical-Subcortical Interaction," John C. Lilly (Virgin Island) and Walter Reitman (Pittsburgh); "Deviance and Drugs," Joseph V. Braddy (Washington, D.C.) and Keither F. Killam, Jr. (Palo Alto); "Irradiation and Generalization," Robert Galambos (Washington, D.C.) and Harry Grunfest (New York); "Psychopharmacology," Orr E. Reynolds (Washington, D.C.) and Amedeo S. Marrazzi (Pittsburgh); and "Inhibition," Paul Hoch (New York) and Louis W. Max (New York).... Listed among the participating scientists of the Academy of Medical Sciences of the Union of Soviet Socialist Republics are: P. K. Anokhin, E. A. Asratyan, P. S. Kupalov, V. G. Rusinov, S. A. Sarkisov, A. V. Snezhnevsky, and V. V. Zakusov.

Epilepsy Center Established in Marseille

About 3 miles from the heart of the bustling French seaport city of Marseille now stands a new, ultramodern structure dedicated to research and treatment problems in the diagnosis, care, and physiopathogenesis of epilepsy, especially of cases arising in early life. Situated at 300, Boulevard Sainte-Marguerite, the center is known as "Centre de Diagnostic Medico Social Pour Epileptiques." The new epilepsy center is under the direction of Professor Henri Gastaut, the Physician-in-Chief. He is aided by well-known figures in neurology (J. Roger and M. Dongier), neuroradiology (G. Salamon), electroencephalography (A. Roger and H. Regis), neurobiology (M. Toga), neurochemistry (C. L. Blanc), pediatric neurology (P. Grimaud), and psychology (S. Dongier). The present resident staff comprises F. Poirier (Ottawa), S. Ouachi (Tunis), and M. Bordas-Ferrer (Asunción, Paraguay). The medical staff is well complemented by social service workers, psychologists, physical therapists, and specialized teachers. Adequate space and modern equipment characterize the clinical and basic science laboratories. An amphitheater with modern projection facilities and numerous conference rooms is ideally situated for the holding of colloquiums, lectures, and conferences. The center, claimed to be unique throughout the world, offers exceptional diagnostic facilities for epileptic children and the opportunity to outline individual

treatment and rehabilitation programs after a short period of study. Patients are returned to referring physicians for long-term care and retraining procedures. In the building itself, living quarters are available for the parents of patients. The idea of the center was originally conceived when Professor Gastaut met in London (October 6 through 12, 1955) with a group of experts selected by the World Health Organization to discuss the problems of juvenile epilepsy in its medical, research, and social aspects. The center officially opened its doors with inaugural exercises on the first of January, 1960. It is supported by the French Public Assistance and by private contributions.

Annual Marseille Colloquium The Ninth European Reunion of Electroencephalographic Information, better known as the "Marseille Colloquium," will be held under the direction of Professor Henri Gastaut at the "Centre de Diagnostic Medico Social Pour Epileptiques," 300, Boulevard Sainte-Marguerite, Marseille (October 11 through 15, 1960). The organization of the sessions will follow the usual Gastaut pattern of a few formal reports but long, intense free discussions. The scientific program is divided into 3 parts: the first is a presentation of privileged observations under the direction of H. H. Jasper (Montreal); the second, a colloquium on EEG changes associated with massive cerebral displacement under the chairmanship of K. J. Zulch (Cologne) and H. Fischgold (Paris); and the third, a colloquium on infantile myoclonic encephalopathies with hypsarythmia under the direction of H. Gastaut, assisted by J. Martin... All communications should be addressed to the Secretariat, Ninth EEG Colloquium, Laboratoire de Neurophysiolgie Clinique, 38, Boulevard Longchamp, Marseille (I^{er}), France.

Chicago Conference on Mental Retardation Sherman E. Kaplitz, Medical Director of The Dr. Julian D. Levinson Research Foundation of Chicago, announces the holding of a mental retardation clinic conference in the LaSalle Hotel, Chicago (October 20 and 21, 1960). Purpose of the conference is to discuss new concepts of mental retardation and to better coordinate the work of the various clinics in this field throughout the United States and Canada and thereby open new avenues of research. The program will feature a panel discussion (October 20) of present concepts concerning mental retardation, chaired by Sherman E. Kaplitz and moderated by Morris Fishbein. The panel members are Ben W. Lichtenstein (neurology); David Yi-Yung Hsia (genetics and biochemistry); Helmer Myklebust (language and psychologic disorders); and Richard Koch (pediatrics). On October 21, there will be a round-table discussion on policies and procedures applicable to the administration of clinics, including staff requirements, intake of patients, diagnostic methods and technics, and follow-up procedures. The final sessions (October 21, P.M.) will highlight

emotional factors in mental retardation, including a presentation by Robert Cooke on neglected areas of research in mental retardation... Communications should be sent to Sherman E. Kaplitz, M.D., Medical Director, The Dr. Julian D. Levinson Research Foundation, 519 S. Wolcott Street, Chicago 12.

Smith Heads Pediatric Neurology at Rochester Dr. Alexandra L. Feldmahn, Assistant Professor of Medicine (Neurology), announces that Wilbur K. Smith has been appointed Professor of Pediatric Neurology at the University of Rochester School of Medicine. Professor Smith has several former students now occupying academic positions in pediatric neurology, notably at the Massachusetts General Hospital, Philadelphia Children's Hospital, and the University of Colorado... The University of Rochester also has a three-year program of approved residency training in neurology, supported by the National Institute of Neurological Diseases and Blindness. This program, which began in July, is under the co-direction of Wilbur K. Smith and Paul A. Garvey. In addition, Rochester provides special facilities for research and advanced training under a special fellowship program. Application for residency appointments can be made at any time.

Briefs The Annual Appropriations Bill for the Department of Health, Education and Welfare contains $560 million for the National Institutes of Health, which is a half-way compromise between the House-approved $455 million and the sum of $664 million which the Senate had voted... G. Milton Shy, Clinical Director of the National Institute of Neurological Diseases and Blindness since 1953, has been named to the new position of NINDB Associate Director in charge of Intramural Research... Warren V. Huber has been appointed Chief of the Neurology Service, Psychiatry and Neurology Division of the Veterans Administration Central Office in Washington... Dr. Carl Robert Brewer, former Chief of the Research Division, U.S. Army Chemical Corps Research and Development Command (Washington, D.C.), was recently appointed Chief of the Research Grants Branch of DGMS at the National Institutes of Health. In his new position, Dr. Brewer will supervise administration of the DGMS program, grants for research, including the Russian Scientific Translation Program and the Clinical Research Facilities Program.

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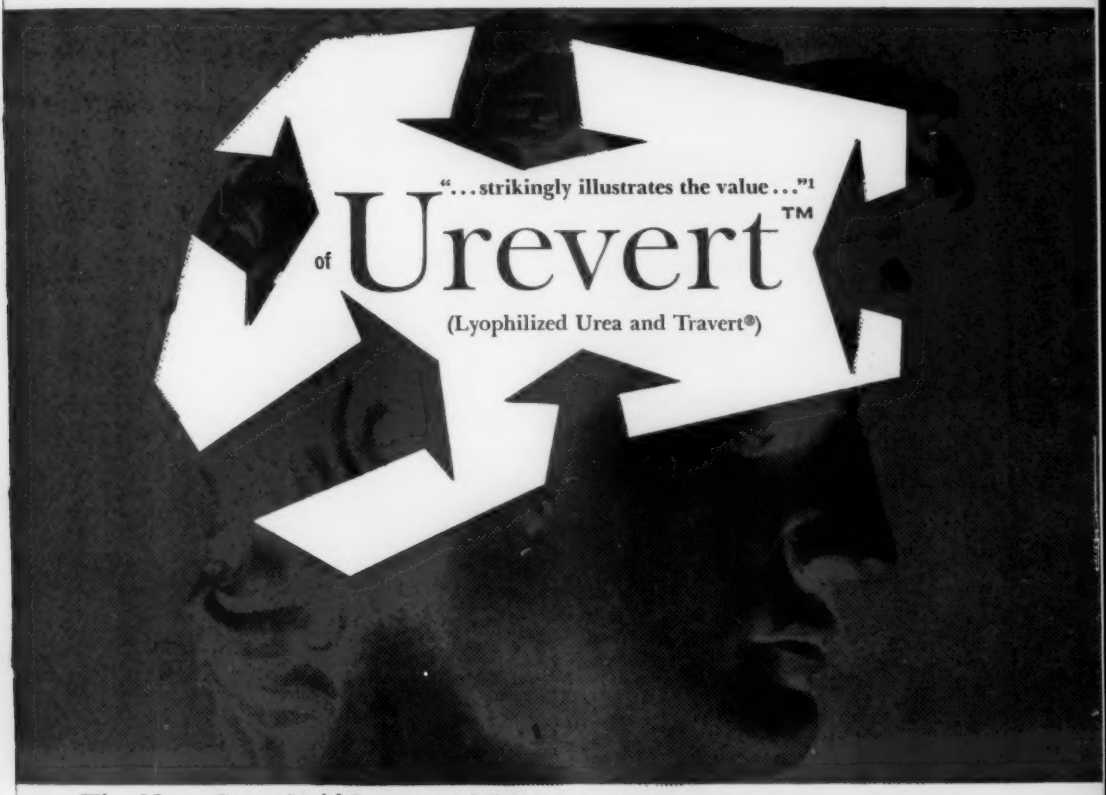

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1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons 32:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

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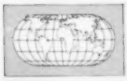

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